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GASTRO-INTESTINAL MANIFESTATIONS OF CARDIOVASCULAR DISEASE

A. Carlton Ernstene, M.D.

Symptoms referable to the gastro-intestinal tract frequently are present in patients with cardiovascular disease and at times are of such prominence that they dominate the clinical picture. Since their misinterpretation may lead to serious errors in diagnosis, proper understanding of the mechanism of their production is of considerable importance. It will be the purpose of this communication to review the pathogenesis of the gastro-intestinal manifestations of cardiovascular disease and to point out the manner in which the correct evaluation of accompanying symptoms and signs will assist in differential diagnosis.

Dysphagia

Dysphagia is an unusual symptom of cardiovascular disease but occasionally it occurs as the result of pressure upon the esophagus by an aortic aneurysm or a greatly enlarged left auricle. Less frequently it is produced by pressure from a large pericardial effusion.

The esophagus is situated in close anatomical relationship to both the aortic arch and the descending aorta, and an aneurysm in either of these portions may exert considerable pressure upon it. Recognition of the cause of the resulting dysphagia is seldom difficult. Aneurysms of the aortic arch may be accompanied by inequality of the pupils, venous congestion of the head and neck, a tracheal tug, dyspnea, disturbances in phonation, and inequality of the radial pulse wave and brachial blood pressure in the two arms. Aneurysms of the descending aorta frequently cause severe pain from pressure upon the spine and nerve roots, and at times they may be responsible for cough and expectoration due to pressure upon the left main bronchus. Roentgen examination of the chest establishes the diagnosis, but it is to be remembered that in ordinary anteroposterior films an aneurysm of the descending aorta may be completely concealed by the cardiac shadow. Radiological study of the heart, therefore, should always include a film taken in the right oblique diameter as well as fluoroscopic examination, and in all individuals in whom dysphagia is present, studies of the esophagus should be made after the administration of thin barium paste.

In patients with mitral valve disease (stenosis, insufficiency, or both) the left auricle is the first chamber of the heart to become enlarged. This enlargement alone may cause very little change in the size of the heart as seen in the anteroposterior diameter, although there usually is an associated prominence of the pulmonary conus. The posterior surface of the heart is comprised principally of the left

auricle, even moderate enlargement of which results in projection of the auricle into the retrocardiac space. The anterior wall of the esophagus normally is in contact with the posterior surface of the heart. Enlargement of the left auricle, therefore, causes displacement backward and occasionally rather sharp angulation of the esophagus. If the auricular enlargement is extensive, the pressure exerted upon the esophagus may result in marked dysphagia, as illustrated in the following case report.

Case 1: The patient, a white married woman, aged 54 years, was admitted to the Clinic on January 6, 1933 because of dyspnea on exertion, difficulty in swallowing, and prominence of the veins of the neck and upper chest. The past medical history was irrelevant except for pneumonia at the age of 19 years, at which time the patient had been ill for three months. In March 1932 fatigability and dyspnea on walking rapidly were first noted. These symptoms increased gradually in severity, and after two months a persistent, slightly productive cough and edema of the ankles developed. Approximately three months before her admission to the Clinic, the patient noted the onset of difficulty in swallowing liquids. Solid food caused no trouble, but every attempt to take liquids resulted in at least partial regurgitation, either immediately or within a few minutes. One month after the appearance of dysphagia, the veins over the neck and chest became prominent and this had increased progressively.

Physical examination revealed a poorly nourished individual who experienced definite dyspnea while at rest. The lips and nail beds were cyanotic. The veins in both sides of the neck, both temporal regions, the anterior wall of the chest, and in the arms were tortuous and engorged. When the patient coughed, a number of small tortuous veins also became visible over the upper back. The heart was considerably enlarged to percussion; its rhythm was regular and the rate 120 per minute. A harsh systolic murmur was heard over the apex, but no diastolic element could be made out. The arterial blood pressure was 122 mm. systolic and 90 mm. diastolic and was the same in both arms. The percussion note was impaired over the base of the right lung and the breath sounds were diminished over this area. A few medium moist râles were heard over the base of both lungs. The liver extended 6 cm. below the costal margin in the midclavicular line and was moderately tender. Slight edema was present over both lower legs. Urinalysis and blood counts revealed nothing of significance. The Wassermann and Kahn reactions of the blood were negative.

An electrocardiogram showed auricular flutter with 2:1 block. Roentgenograms of the chest in the anteroposterior diameter revealed enlargement of the heart with calcific deposits in the pericardium (Fig. 1). Films taken in the oblique diameter after the administration of barium paste by mouth showed obstruction of the esophagus due to pressure from an enlarged left auricle (Fig. 2). Fluoroscopic examination revealed greatly diminished cardiac pulsations.

It is of considerable interest that with absolute rest in bed and the administration of digitalis, the patient's dysphagia disappeared entirely within one week.

Anorexia, Nausea, and Vomiting

Anorexia is a common symptom in patients who have slight or moderate congestive heart failure, and in individuals with advanced

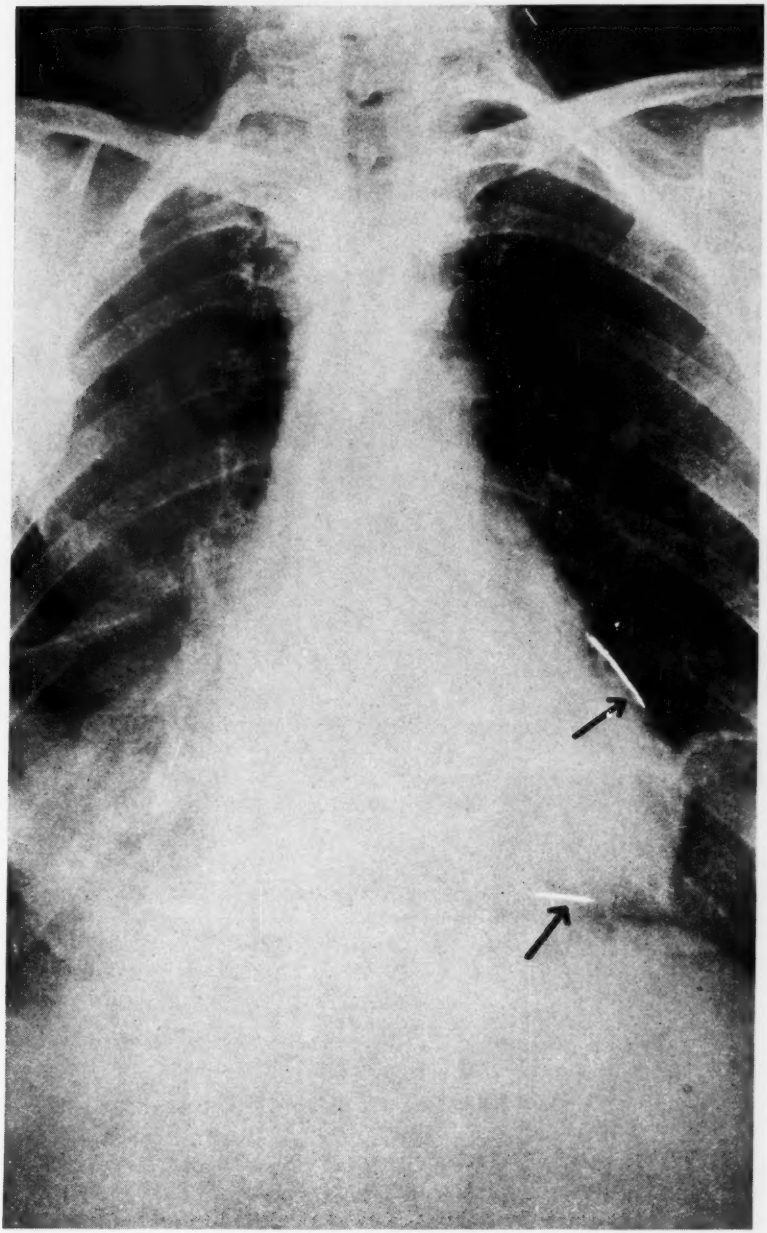

FIGURE 1: Case 1: Anteroposterior view showing enlargement of heart and calcified areas in the pericardium. (The areas of calcification have been retouched to show their location more clearly.)

FIGURE 2: Case 1: Oblique view showing calcified area in pericardium and compression of the esophagus. (The areas of calcification have been retouched to show their location more clearly.)

failure there often is persistent nausea and repeated vomiting. In addition, many patients with congestive failure complain severely of flatulence. At times these symptoms may be of sufficient prominence and so far out of proportion to such symptoms as dyspnea and cough that a diagnosis of some form of primary gastro-intestinal disease is suggested. The symptoms are due to passive congestion of the gastric and intestinal mucosa and of the liver. Careful physical examination usually leads to proper interpretation of the patient's complaints. The heart is usually enlarged and its rhythm frequently is irregular. There generally is evidence of more or less extensive passive congestion of the lungs. The jugular veins are engorged and remain distended even when the patient is propped up in bed; the liver is enlarged and tender, and there is a variable degree of edema of the legs and over the lower back.

Not infrequently a patient with congestive heart failure is first seen only after he has been under the care of another physician for some time. The patient may or may not know what medication he has been receiving, and the question arises whether the anorexia, nausea, and vomiting have resulted from overdosage with digitalis. Fortunately, there are a number of points in the history and physical examination that usually enable one to make an accurate decision. In the first place, a description by the patient of the medicines he has taken and the dosages may be helpful. Secondly, if the patient has received sufficient digitalis to produce toxic symptoms he usually will report that there was decided improvement in the symptoms of myocardial failure after he began to take medicine and before anorexia or nausea and vomiting developed. If auricular fibrillation is present and the ventricular rate is very rapid, one may safely conclude that the patient has not had too much digitalis while the same arrhythmia with a ventricular rate of 60 or less suggests that large amounts of digitalis have been given. Frequent premature beats and especially bigeminal rhythm due to regularly recurring premature beats also increase the probability of digitalis overdosage. In general, however, it will be found that in the individual who presents objective evidence of congestive heart failure, anorexia, or nausea and vomiting are the result of heart failure rather than digitalis intoxication. Under such circumstances the administration of more digitalis often results in prompt and complete relief from the gastro-intestinal symptoms.

A sensation of distention or gas in the upper abdomen is a not infrequent complaint of individuals with coronary artery sclerosis, and occasionally repeated attacks of nausea and vomiting constitute one of the chief symptoms of the disease. Symptoms of this kind often cause the patient to diagnose his condition as "indigestion," but careful

questioning and thorough physical examination usually reveal things in their proper light. In all but the exceptional case, a history of relationship between the appearance of symptoms and exertion or emotional upsets will be present. Many patients will have observed that although even moderate activity soon after eating will cause symptoms, all discomfort can be avoided by limiting the size of the meal and by resting after eating. Furthermore, although there may be no actual pain in the substernal area during the time that symptoms are present, there almost always is at least a sensation of fullness, pressure, or gas in this location. Rest usually affords prompt relief from the symptoms, and vomiting, when it occurs, has a similar effect. Nitroglycerine also has a specific effect. On examination, the heart may or may not be enlarged, and its rhythm usually is regular. The arterial blood pressure frequently is elevated, and electrocardiograms often reveal evidence of coronary artery disease.

The following case report illustrates the manner in which vomiting may comprise an important part of the symptomatology of coronary artery disease.

Case 2: A white man, a musician, aged 68 years, was first seen on December 19, 1935, because of attacks of severe pain or pressure in the upper substernal area accompanied at times by forceful, almost projectile vomiting without preceding nausea. The first seizure had occurred one month earlier, and four of the five attacks that had been experienced had been brought on by exertion. In two attacks, relief had been obtained by resting for a few minutes, but in the other three the pain had persisted until the sudden onset of vomiting about thirty minutes later. All seizures had been accompanied by moderate dyspnea. There had been no radiation of the pain from its upper retrosternal location.

Physical examination revealed a well developed, well nourished, anxious individual. The pupils were equal, regular, and reacted normally. The heart was not enlarged, and its rate and rhythm were normal. There were no murmurs. The peripheral arteries showed advanced diffuse sclerosis, and the blood pressure was 192 mm. systolic and 104 mm. diastolic. The lungs were clear on percussion and auscultation. Abdominal examination revealed no areas of tenderness and no palpable masses or solid organs.

The three conventional leads of the electrocardiogram showed no evidence of myocardial damage but in precordial leads, the T waves were upright. Roentgen examination of the thorax revealed no evidence of pathologic change in the heart, aorta, or lungs. Roentgen examination of the gastro-intestinal tract also gave normal findings. Examination of the gastric contents after the administration of an Ewald meal showed normal concentrations of free and total acid. It was concluded, therefore, that the vomiting was due directly to coronary artery disease.

In spite of medication and a prolonged period of rest in bed with subsequent strict limitation of activity, the attacks of pain continued to occur with increasing frequency, and developed more and more often while the patient was at rest. Many nocturnal seizures were experienced. Nitroglycerine never failed to give relief within a few minutes, but if for some reason nitroglycerine was not

taken, almost explosive vomiting usually occurred within one-half hour and brought the attack to an end. The patient died on May 15, 1936, two hours after the onset of symptoms of acute coronary occlusion.

Nausea and vomiting often develop soon after the onset of acute coronary artery occlusion. Pain, however, is the outstanding symptom, and the differentiation between coronary occlusion and upper abdominal disease will be discussed from this viewpoint later.

Jaundice

The bilirubin content of the blood is increased in practically all cases of congestive heart failure, and occasionally this increase is sufficient to produce visible jaundice. Icterus, when it occurs, is the result of two factors. The first of these is depression of the excretory function of the liver due to the anoxemia which results from passive congestion. The second is increased production of bilirubin as evidenced by its increased concentration in the blood and its increased excretion as urobilin in the stools and urine.

Passive congestion of the liver due to causes other than myocardial failure may also result in the appearance of icterus. Extensive pericardial effusion, for example, is accompanied by increased peripheral venous pressure, congestion of the viscera, and occasionally by jaundice.

When jaundice develops quickly in patients with congestive heart failure, or rapidly becomes more intense after having been present for some time, the change is usually due to pulmonary infarction. Infarction of the lung causes a sudden increase in the degree of anoxemia of the liver and reduces the already impaired excretory function of the hepatic cells. In many instances, the increased anoxemia causes actual necrosis of the liver cells in the center of the lobules.

The following case report illustrates the occurrence of jaundice in congestive heart failure with rapid intensification due to pulmonary infarction.

Case 3: The patient was a white male, forty-six years of age, who had had chronic cough and dyspnea on exertion for ten years. During the week before admission to the hospital these symptoms had increased and edema of the legs had been present. On physical examination, there was orthopnea, moderate cyanosis, and slight jaundice. The heart was enlarged with systolic and diastolic murmurs at the apex. Auricular fibrillation was present. There were signs of congestion at the base of both lungs and of consolidation in the left midchest posteriorly. The liver extended almost to the level of the umbilicus, and there was edema of the legs and over the lower back.

During the first two days in the hospital, the jaundice increased greatly. Then for twelve days it gradually diminished as the patient's general condition improved. On the fourteenth day, however, there was an abrupt increase in dyspnea and cyanosis, and on the following day the jaundice was noted to be much more intense. There had been no cough, pain in the chest, or hemoptysis,

and examination of the chest revealed no significant changes in the physical findings. The patient became comatose and died two days later. During the entire period of observation, bilirubin had been present in the urine, but the stools had been of normal color.

Necropsy confirmed the diagnosis of rheumatic heart disease with mitral stenosis. The liver was enlarged and congested and showed necrosis of the central cells of the lobules in microscopic sections. The major portion of the cavity of the left auricle was occupied by a large, grayish-red, friable thrombus, and the lumen of the right inferior pulmonary vein was occluded by an attached thrombus which extended peripherally for a considerable distance along its tributaries. The lower lobe of the right lung was completely infarcted; it was deep red in color and of a firm, rubbery consistency throughout. Scattered through the remainder of the lungs were many areas of thrombotic infarction, ranging from a few millimeters to 5 or more centimeters in diameter. There were no areas of pneumonia.

Prolonged febrile illnesses which are accompained by the development of severe anemia cause atrophy of the central hepatic cells and depress the excretory function of the liver. At the same time, the increased destruction of red blood cells results in a considerable increase in bilirubin production, and jaundice may therefore appear. In subacute bacterial endocarditis, the skin often has a diffuse, yellowish-brown color to which the term "café au lait" is applied. Occasionally, if the disease is accompanied by sufficiently severe anemia, the skin and sclera becomes definitely icteric.

Jaundice occasionally develops within the first two or three days after the occurrence of acute coronary occlusion. Usually the icterus is of only slight degree but at times it becomes quite deep. The liver is generally enlarged and tender, and in all probability the development of jaundice is to be explained as a result of anoxemia of the hepatic cells.

Abdominal Pain

A number of cardiovascular conditions may cause abdominal pain. Patients with advanced congestive heart failure often complain of discomfort or actual pain in the epigastrium and right upper quadrant of the abdomen due to the presence of an enlarged, congested liver. Recognition of the cause of the symptoms is a simple matter under such circumstances, and in favorable cases the institution of proper treatment results in prompt relief.

Although the pain of angina pectoris is typically retrosternal in location, it may occasionally be situated in the epigastrium. In general the differentiation of pain of this kind from that due to abdominal disease is not difficult. The relation of the pain of angina pectoris to exertion and its prompt subsidence with rest is of fundamental importance. Furthermore, although the pain may not spread beyond its epigastric location if the patient becomes inactive with the first appearance of dis-

comfort, it is much more common to have some radiation to the retrosternal area or at least an accompanying sensation of fullness, pressure, or tightness in this region. Physical examination in the patient with angina pectoris may reveal nothing of diagnostic significance, and the electrocardiogram may also fail to help. The ultimate diagnosis, therefore, must often be based upon a careful analysis of the patient's symptoms.

Early writers on coronary thrombosis directed attention to the fact that the disease might closely simulate surgical conditions in the upper abdomen, and the possibility of erroneously attributing the symptoms of coronary occlusion to upper abdominal disease has since been emphasized repeatedly. The pain of coronary thrombosis may be situated entirely in the upper abdomen for several hours, and on examination there may be muscle spasm and tenderness in the epigastrium or right upper quadrant. These findings and the occurrence of fever, leukocytosis, vomiting and at times jaundice may very strongly suggest biliary colic, perforated peptic ulcer, acute intestinal obstruction, or acute pancreatitis. An error in diagnosis usually can be avoided, however, by careful attention to the clinical history and to other points in the general physical examination. A large proportion of patients who have coronary thrombosis have had earlier attacks of typical angina pectoris, and in others there will be a history of "indigestion" on effort. The pain of coronary occlusion usually is accompanied by dyspnea while dyspnea is not commonly present in patients who have acute surgical conditions in the abdomen. Furthermore, although the pain of coronary thrombosis may be confined to the epigastrium for several hours, it is much more common to have at least some spread to the retrosternal area within a short time of its onset. Radiation of this kind does not occur in abdominal disease. Physical examination soon after the onset of coronary thrombosis frequently reveals great weakness of the heart tones, and gallop rhythm is often present. Pulsus alternans may be detected while recording the blood pressure, and in patients with extensive cardiac infarction, râles may appear over the base of the lungs within a very short time. A pericardial friction rub is detected in 10 or 15 per cent of all patients with myocardial infarction and usually develops within one to three days after the onset of symptoms. Its occurrence in patients who have experienced symptoms that might be due to coronary thrombosis furnishes a valuable diagnostic sign. Finally, the electrocardiogram may show pathognomonic evidence of coronary occlusion within a few hours of the onset of symptoms.

A few words of caution might well be introduced at this place. In the past, in discussions of the differential diagnosis of angina pectoris and coronary occlusion, emphasis has been placed almost entirely upon the

fact that these conditions may closely simulate upper abdominal disease. Of late, however, a few observers have pointed out the possibility that errors may be made in the reverse direction and have reported cases in which symptoms due to gallbladder disease, perforated peptic ulcer, or diaphragmatic hernia suggested coronary artery disease. In the great majority of cases, the presence of angina pectoris or coronary thrombosis is correctly recognized, but as the result of the popularity of these diagnoses, other diseases with similar symptoms undoubtedly are being included at times under the same classifications. Although such errors are not common, they are of importance because of their bearing on prognosis and treatment.

There are a few other cardiovascular conditions which may cause severe abdominal pain. Chief among these are aneurysm of the abdominal aorta and infarction of the kidneys, spleen, or mesentery due to emboli from the heart. Aneurysm of the abdominal aorta is of rare occurrence but may cause pain, usually constant and boring in character and often very severe, due to pressure upon the spine and nerve roots. The two most common cardiac conditions which may be complicated by embolic infarction of abdominal structures are bacterial endocarditis with the development of large friable vegetations upon the heart valves and endocardium, and coronary occlusion with infarction of the heart and the secondary formation of a mural thrombus over the endocardial surface of the myocardial infarct. Occasionally also, embolic accidents occur in patients with mitral stenosis and auricular fibrillation. In these patients the auricular appendages often contain thrombotic material, portions of which may be broken off and lodge in any part of the pulmonary or systemic circulation.

Infarction of the spleen, kidneys, or mesentery complicating bacterial endocarditis seldom causes confusion in diagnosis. The history of a febrile illness of variable duration, the occurrence of petechiae in the skin or conjunctivae and the presence of cardiac murmurs generally lead to prompt recognition of the primary condition, and the obtaining of a positive blood culture establishes the diagnosis beyond doubt. Embolic accidents which complicate coronary occlusion occur most commonly during the second week after the attack but may occur up to the sixth or eighth week. Under unusual circumstances it may happen that the symptoms of coronary occlusion are of such mildness that their significance is not appreciated by the patient or the physician. The development of severe abdominal pain at some time during the following few weeks may then present a difficult problem and may lead to an erroneous diagnosis of acute intestinal obstruction, acute pancreatitis, or perforated peptic ulcer. A careful review of the clinical history, however, should enable one to avoid such a mistake. Embolic accidents

which occur in patients with mitral stenosis and auricular fibrillation seldom offer difficulty in diagnosis if the possibility of this complication is kept in mind.

Summary

Dysphagia, anorexia, nausea, vomiting, jaundice, and abdominal pain are not infrequently due to cardiovascular disease. Dysphagia due to compression of the esophagus may result from aneurysm of the aorta, marked enlargement of the left auricle in mitral valve disease, or extensive pericardial effusion. Anorexia, nausea, and vomiting are common manifestations of congestive myocardial failure and are due to congestion of the liver and the mucosa of the stomach and intestinal tract. Nausea and vomiting may also constitute a prominent symptom of coronary artery disease and especially acute coronary artery occlusion. Jaundice in patients with heart disease is the result of anoxemia of the liver cells and may occur in congestive heart failure, coronary thrombosis, and occasionally in subacute bacterial endocarditis. Abdominal pain due to congestion of the liver is present in many patients with congestive heart failure, while in angina pectoris and coronary occlusion the pain may be confined entirely to the upper abdomen. Severe abdominal pain may also result from an aneurysm of the abdominal aorta and from infarction of the spleen, kidneys, or mesentery due to emboli which arise from the vegetations of bacterial endocarditis, a mural thrombus secondary to myocardial infarction, or from thrombi in the left auricular appendage in patients with mitral stenosis and auricular fibrillation. While, at times, any of these symptoms may sufficiently dominate the clinical picture to suggest primary gastro-intestinal disease, attention to the details of the clinical history and a thorough physical examination usually enable one to make a correct diagnosis.

GASTRO-INTESTINAL SYMPTOMS OF LESIONS IN THE GENITO-URINARY TRACT

W. J. Engel, M.D.

An old teacher of mine once said, " You cannot diagnose anything that you don't think of." The purpose of this paper is to direct attention to certain genito-urinary lesions which may give rise to pronounced gastro-intestinal symptoms and to encourage more consideration of the urinary tract in the differential diagnosis of what appear to be acute conditions of the abdomen.

Many patients with relatively acute gastro-intestinal symptoms do not require immediate surgical treatment and a good many others who have gastro-intestinal symptoms do not have clear-cut intraperitoneal disease, and it is this group particularly that deserves further investigation.

Dr. C. L. Hartsock of the Clinic, in a recent review of patients presenting themselves with gastro-intestinal symptoms, found that in only 35 to 50 per cent could the cause be actually demonstrated in the gastro-intestinal tract, and in 20 per cent of the patients one might expect to find outside the gastro-intestinal tract the lesions producing the symptoms. From the urologist's point of view, it is interesting to note that approximately 30 per cent of patients with lesions of the kidneys and ureters may be expected to have associated gastro-intestinal symptoms and, in our experience, from 17 to 20 per cent have had abdominal operations previously without relief of symptoms. This shows the importance of a careful preoperative diagnosis, not only in preventing unnecessary surgical procedures but in securing good results from the operative procedures which are carried out.

The most common gastro-intestinal symptom associated with lesions of the genito-urinary tract is nausea with or without vomiting. In many instances, the nausea and vomiting is extremely intense and, when the patient is seen in this condition, the natural inclination is to place the blame on some gastro-intestinal disease. In addition to this, however, pain may be referred to the abdomen. If the lesion exists in the kidney and upper part of the ureter, the pain is most commonly referred to the epigastrium or one of the upper quadrants of the abdomen. If, on the other hand, the pathology in the urinary tract is in the lower part of the ureter, the pain is usually referred to the corresponding lower segment and reflex disturbance is more likely to affect the lower part of the intestinal tract. Of course, it is well known that lesions at the extreme lower end of the ureter, particularly stones, may cause pain to the external genitalia.

The explanation for the occurrence of gastro-intestinal symptoms in lesions of the urinary tract lies in the common nerve supply of the two organs. The nerves of the kidney are derived from the renal plexus which is formed by contributions of the solar and aortic plexus and the last splanchnic nerve. The renal plexus accompanies the renal artery which it surrounds in a meshwork of fibers and proceeds to the pelvis of the kidney and its small branches are sent out to the capsule. Both the renal and abdominal sympathetic plexes are therefore derived in part from the solar plexus. It is thus readily understood how lesions in the urinary tract may reflexly affect the gastro-intestinal tract through nerve communications in the solar plexus and the abdominal sympathetics.

It has been shown experimentally that changes in muscular activity of the digestive tube occur as the result of stimulation of the kidneys and ureters. These consist of an increase in frequency and amplitude of gastric peristalsis and an atony and inhibition of peristalsis in the colon. This coincides with the clinical picture one sees in these cases.

The most common lesion of the urinary tract which gives rise to gastro-intestinal symptoms is that of calculous disease. In a series of patients with ureteral stone which we recently studied, it was found that 20 per cent of the patients had had previous abdominal operations, the majority being appendectomies, and an additional 16 per cent had had erroneous diagnoses without operations. Cecil reports that his study of patients with kidney or ureteral stones showed that the pain was limited to the abdomen alone in 20 per cent of the cases, and in 19 per cent other abdominal operations had been performed without relief of symptoms.

Our experience has been that small stones impacted at the lower end of the ureter give rise to the most severe and alarming gastro-intestinal symptoms. The stone which is present in the kidney pelvis, if it does not give symptoms directly referable to the kidney, is much more likely to give rise to symptoms of chronic dyspepsia and low-grade pain in the upper part of the abdomen.

The following brief reports of patients serve best to illustrate these points.

Case 1: The first patient was a man, 45 years of age, who was referred to the Clinic with the diagnosis of acute intestinal obstruction. He had had an appendectomy several years previously and two days before admission to the hospital he had been seized with sudden, severe pain in the right lower abdominal quadrant. Nausea and vomiting immediately followed and within a few hours there was abdominal distension. The nausea and vomiting persisted and the vomitus became fecal in nature.

Examination showed that he was not acutely ill although he appeared rather toxic and dehydrated. There was rather pronounced abdominal distension without visible peristalsis. There was some tenderness in the right

costovertebral angle and this led us to suspect obstruction of the right urinary tract. A cystoscopic examination was therefore carried out and, upon catheterizing the right ureter, a slight, temporary obstruction was encountered about 3 cm. from the ureteral orifice. The ureteral catheter, however, passed this obstruction and there immediately was a very rapid flow of retained, bloody urine. A roentgenogram showed a very small shadow at the extreme lower end of the ureter.

A catheter was left in the kidney for continuous drainage and within a few hours the patient's vomiting stopped completely. The abdominal distension disappeared and the patient became entirely comfortable. Three days later the ureter was again catheterized and crystal-clear urine was obtained from the pelvis of the kidney. The patient was dismissed from the hospital entirely well, four days after admission.

Case 2: Another similar case was that of a man, 39 years of age, who was brought to the hospital complaining of pain in the left lower abdominal quadrant, abdominal distension, chills, and fever. He had been confined to a hospital in his home town for twelve days and a diagnosis of an acute abdominal condition of undetermined origin had been made. Quinine therapy and hot applications had been administered and these had caused slight improvement but the pain, chills, and fever had persisted.

At the time of admission, the temperature was 101.6° F. and there was severe pain in the left lower quadrant of the abdomen. The abdomen was markedly distended and there was severe nausea and vomiting. Further examination revealed some tenderness in the left costovertebral angle so we had a plain roentgenogram made which showed a shadow in the region of the lower part of the left ureter. Cystoscopic examination was therefore carried out, and on passing the catheter up the left ureter, an obstruction was met about 4 cm. from the ureteral orifice but it was passed and, upon reaching the pelvis of the kidney, a large amount of very thick, purulent urine was obtained. The catheter was left in place for drainage, following which the temperature immediately began to drop, and within a few hours the pain was entirely relieved and the nausea and vomiting ceased. A few days later a left ureterolithotomy was done. The patient had an uneventful convalescence and was entirely well when he was discharged from the hospital eight days following the operation.

That stones in the kidney may give rise to a somewhat different train of symptoms is illustrated by the following case.

Case 3: A man, 31 years of age, was admitted complaining of periodic attacks of pain in the right upper quadrant with radiation to the right lower quadrant. He stated that he had had intermittent attacks for a period of 17 years, and 12 years previously an appendectomy had been performed. The pain recurred and five years later an abdominal exploration was performed for adhesions, but again the symptoms returned. The patient had lost 15 pounds in weight, his appetite was very poor, and he frequently experienced nausea without vomiting. A plain roentgenogram was made which showed the presence of a large calculus in the right kidney. Following a pelviolithotomy he had complete relief of symptoms, gained 17 pounds in weight, and has remained well since his operation a year and a half ago.

The diagnosis in patients such as these is sometimes confusing because, by the time the physician is called, the gastro-intestinal

symptoms so completely dominate the patient's illness that lesions outside the digestive tract are not considered in the differential diagnosis. Frequently a lead to the correct diagnosis may be had by eliciting a careful history. In most cases, careful questioning will reveal the fact that there was definite kidney pain previous to the onset of nausea and vomiting. It is well known that in obstructive lesions of the urinary tract, the distension of the kidney pelvis and pressure on the capsule give rise to pain, and this must necessarily exist before reflex gastro-intestinal symptoms begin. Therefore, one should get a lead to the correct diagnosis by obtaining a history of pain in the flank previous to the onset of gastro-intestinal symptoms.

The next most common lesion of the urinary tract which produces gastro-intestinal symptoms is hydronephrosis. Of course, a good many of these are in turn due to kidney or ureteral stones, yet there are other types of hydronephrosis, particularly those associated with obstructive lesions at the ureteropelvic junction, in which the diagnosis may be extremely confusing owing to the absence of any positive urinary findings. In a group of cases of hydronephrosis which we studied, 23 per cent of the patients had nausea and vomiting, and in a series of 52 cases of hydronephrosis associated with aberrant artery, 26 per cent had been treated for gastro-intestinal disease and 17 per cent had had previous abdominal operations without relief of their symptoms. Here again, nausea and vomiting is the most common associated symptom, although in this type of condition there may be abdominal pain which is extremely difficult to diagnose. This is particularly true if the hydronephrosis involves the right kidney, for the right upper quadrant of the abdomen is indeed a diagnostic pitfall owing to the multiplicity of lesions which may produce pain in this location. The following case illustrates these points.

Case 4: A young man, 21 years of age, was admitted complaining of periodic attacks of pain in the right upper quadrant of the abdomen associated with nausea and vomiting. The attacks might last for a day or two at a time and then subside, recurring again at irregular intervals. The pain at times radiated into the right lower quadrant but there was no history of fever with the attacks. An appendectomy had been performed a year previously but the symptoms had returned. A plain roentgenogram revealed no abnormalities. It was decided, however, that the kidneys should be investigated and a cystoscopic examination and ureteral catheterization were done. The pyelogram showed hydronephrosis of the right kidney with the kettle drum type of pelvis indicating an aberrant artery. Operation was advised and an obstructing aberrant artery was found which was divided and the ureter freed. This patient has experienced complete relief from symptoms since operation three years ago.

Urinary infections are not infrequently associated with gastro-intestinal symptoms. Tuberculosis of the kidney does not commonly give rise to diagnostic difficulty and yet the following case serves to

illustrate an instance in which a diagnosis of tuberculosis was not made for a considerable period of time.

Case 5: A young man, 28 years of age, had had attacks of pain in the left side for a period of eighteen months. The physician who was attending him stated that at the time of the original severe attack, there was a definite tumor mass which was palpable in the left lower abdomen. This was associated with abdominal distension, nausea, and a high fever. The physician believed that these symptoms were in all probability due to diverticulitis of the colon. The original attack subsided and the patient improved but soon had recurrent attacks of the same nature. When the patient was referred to the Clinic for examination, he was acutely ill and a definite mass was palpable in the left flank which was extremely tender. The unusual feature of this particular case was the fact that no urinary symptoms developed until a few days before admission into the hospital, at which time frequency and burning on urination were present.

Cystoscopic examination was carried out and a rather pronounced cystitis without ulceration was seen. The left ureter was catheterized and a considerable amount of purulent urine obtained. A pyelogram of the left side showed a deformity typical of renal tuberculosis and operation was advised. At operation, in addition to the tuberculous kidney, a very extensive perirenal inflammatory mass was encountered.

In this particular case, therefore, the patient had apparently had repeated peri-ureteral and perinephritic infections which had given rise to the mistaken diagnosis of a lesion of the descending colon.

It is, of course, well known that other acute infections of the kidney may give rise to gastro-intestinal symptoms. It is a common picture for patients with acute pyelitis to have some nausea and vomiting at the height of their fever. Usually in such cases there is no mistaken diagnosis, however, because urinalysis immediately directs attention to the infectious process in the kidney.

Rarely, kidney tumors will give rise to gastro-intestinal symptoms, as illustrated by the following case:

Case 6: A woman, 47 years of age, came into the Clinic for examination, having been advised to have an appendectomy for pain in the right side of the abdomen. A careful history elicited the fact that she had had occasional attacks of hematuria for the past year, the bleeding lasting only a very short time and clearing up spontaneously. The significant fact was that her attacks of pain usually occurred at the time of bleeding, but the pain was in the right side of the abdomen and referred to the region of the umbilicus. There had been no vomiting.

In view of this history, we felt that investigation of the right urinary tract was demanded and a pyelogram of this kidney showed a filling defect typical of kidney tumor. The kidney was removed and was found to be the seat of an adenoma.

It is quite likely that, in this case, the pain that the patient had been experiencing was due to the passage of small blood clots down the ureter, thus producing temporary ureteral obstruction.

Occasionally, one encounters congenital anomalies of the urinary tract which give rise to gastro-intestinal symptoms. This is best illustrated by the following case:

Case 7: A young woman, 29 years of age, entered the Clinic in August, 1934. Her chief complaint was of pain in the right lower quadrant of the abdomen associated with nausea, vomiting, and loss of weight. Her symptoms were approximately of eight years duration. The nausea and vomiting were most intense and at times lasted for a week or ten days, necessitating hospitalization for the intravenous administration of fluids in order to sustain life. Soon after the original onset of symptoms, an appendectomy had been performed following which the patient was partially relieved for a few months. The symptoms recurred, however, and a few years later a cholecystectomy was done without any relief of symptoms. Later, at a third operation, the pelvis was explored and she was told that some ovarian cysts were punctured. In spite of these numerous surgical attacks, the patient's pain continued as did the terrific episodes of nausea and vomiting.

This patient was first seen in the Diagnostic Department and was referred to the Genito-Urinary Department for investigation of the urinary tract. At the time of cystoscopic examination, catheterization of the right ureter reproduced the pain, but the right pyelogram showed a normal kidney pelvis and there was no evidence of stone. We believed that this was a ureteral stricture and advised that she return for dilatation. At the second cystoscopic examination, a small dimpling was seen immediately below the right ureteral orifice. This had not been apparent at the time of the first cystoscopic examination and, in order to explore it, I probed with a small ureteral catheter and found that the catheter passed up 5 or 6 cm. This reproduced the patient's agonizing pain. It was impossible to fill this ureter with contrast media as the introduction of even a few drops of solution produced intolerable pain. A diagnosis of aberrant ureter was made and, owing to the accurate reproduction of the symptoms by catheterization, operation was advised. Because she had had so many operations, she was naturally loathe to accept this advice and returned to her home. Soon after, however, she had another extremely severe episode of pain, nausea, and vomiting, and returned for the operation.

At operation the aberrant ureter was located, divided at the bladder, and upon tracing it upward, it was found to end blindly at the lower pole of the right kidney. During the operation, marked hyperperistalsis in this ureter was observed and at the extreme upper end numerous filamentous communications extended from the upper end toward the pelvis of the kidney, these undoubtedly being nerve communications. The removal of this aberrant ureter completely relieved the patient's symptoms and within a few months she had gained 20 pounds in weight. She has been seen periodically since that time and has remained perfectly well.

It is particularly significant in this case that histologic sections of this ureter showed it to be entirely normal without any infection or other demonstrable change. It seems that one can explain this pain, therefore, only on the basis of hyperperistalsis of the aberrant ureter which produced extreme reflex disturbances in the gastro-intestinal tract.

Another congenital type of lesion which frequently produces gastro-intestinal symptoms is horseshoe kidney. The following case illustrates this:

Case 8: A woman, 50 years of age, was admitted complaining of periodic attacks of pain in the lower left quadrant. This had been associated with rather marked constipation and on numerous occasions the patient had had mucus and some blood in the stools. A diagnosis of colitis had been made and she had been treated, but without relief of symptoms. Investigation of the urinary tract disclosed the fact that she had a horseshoe kidney, the left half of which was hydronephrotic and very low lying, being practically a pelvic kidney. Operation was carried out, and the left half of the horseshoe kidney was removed. The patient has had complete relief of her symptoms and the bowel condition has entirely cleared up.

These remarks and a brief review of cases illustrate the common association of gastro-intestinal symptoms in lesions of the urinary tract. It is not contended that every patient with gastro-intestinal symptoms should have complete investigation of the urinary tract, and yet if one carries out urologic investigation in all confusing or long standing cases of this type, one will be surprised to find what a high incidence of diseases in the genito-urinary tract will be demonstrated.

TUMORS OF THE SPINAL CORD

A. T. Bunts, M. D.

Although not common, primary tumors involving the spinal cord merit consideration for two important clinical reasons: In diagnosis they are often mistaken for other more common conditions, with consequent errors in treatment and serious results due to delayed surgical intervention. In our experience[1], about 50 per cent of these tumors prove to be of such a nature that they may be removed completely and a favorable prognosis given as regards life and restoration of normal function.

Any part of the spine or of the contents of the spinal canal may be the site of origin of a neoplasm. Various types of bone tumors and cartilaginous tumors may arise from the vertebrae and intervertebral disks and cause compression of the spinal nerve roots or of the spinal cord. Lipoma or sarcoma of the epidural connective tissue may occur. Angiomatous tumors may arise from extradural blood vessels or from those of the cord itself. The most common primary tumors are the neurofibroma which arises from the spinal nerve roots, the meningioma which arises from the meninges, and the glioma originating in the glial tissue of the spinal cord. Other less common tumors are the congenital dermoid and the pigmented nevus. Metastatic lesions from primary malignant tumors in other parts of the body may lodge in the spine and give rise to symptoms simulating those of primary spinal cord tumor. These, therefore, must be considered also in differential diagnosis. The breast, the prostate, and the kidney (hypernephroma) are the most common primary sites for such neoplasms.

The symptoms of spinal cord tumor are the result of involvement of sensory or motor nerve roots or of the cord itself. Inasmuch as the cord and its nerve roots lie within the spinal canal from the foramen magnum to the lower end of the spine, it is evident that symptoms may be referred to any part of the body, except to the anterior half of the head. In adults, the spinal cord terminates at the level of the lower end of the first lumbar vertebra, below which the spinal canal contains the long nerve strands, so grouped as to merit the descriptive name of "horse's tail." Tumors of the cauda equina, therefore, give rise to symptoms of involvement of the lumbar and sacral nerves but not to symptoms of compression of the spinal cord.

Pain, disturbances of sensation, disorders of motion in the legs or arms, and dysfunction of the vesical and anal sphincters are the chief symptoms caused by spinal cord tumors. Any of these symptoms may occur independently of the others or in association with one or more of

the others. Pain is the earliest and most common symptom of spinal cord tumor and may be present for many months or even for several years before symptoms of compression of the cord ensue. This is particularly true in the case of the slow-growing, benign, extramedullary tumors, such as the neurofibroma and the meningioma. By irritation of sensory nerve roots, such tumors give rise to pain which may be referred along the course of distribution of the nerve. This so-called "root pain" is often severe and may be mistaken for the pain of angina pectoris, intercostal neuralgia, neuritis, arthritis of the spine and sacro-iliac joints, gallstones, renal and ureteral stones, lesions of the gastro-intestinal tract, and "sciatica." In some instances, needless abdominal and pelvic operations have been performed for the relief of pain caused by spinal cord tumors. Pain may also occur in the spine at the site of the tumor and is often more noticeable at night. Sneezing, coughing, or straining at stool may increase the pain caused by a spinal cord tumor.

Progressive alterations in motor and sensory functions accompany the growth of a tumor as it produces compresson of the spinal cord. The more common clinical manifestations are difficulty in gait, weakness and spasticity of the legs due to changes in the pyramidal tracts of the cord, and numbness or paresthesiae of the legs and trunk due to involvement of the sensory tracts of the cord. Obviously, if the tumor is located in the cervical region, it may give rise to similar phenomena in the arms in addition to those in the lower extremities.

Control of the anal and vesical sphincters may be disturbed in the presence of spinal cord tumors, and impotence or inability to ejaculate may occur in man. These phenomena are observed commonly in cases of intramedullary tumor and tumor involving the conus medullaris at the lower end of the cord and the cauda equina.

Diagnosis: After a thorough general physical examination has been made, together with routine blood counts, blood Wassermann reaction, and urinalysis, the following procedures are of major importance in the study of a patient who is suspected of harboring a tumor of the spinal cord.

1. Neurological examination.
2. Roentgenograms of the spine.
3. Lumbar puncture and Queckenstedt's test, including examination of the cerebrospinal fluid.

Neurological examination may reveal weakness or spasticity of one or more extremities, hypesthesia or anesthesia of the skin, and changes in the tendon, abdominal, and cremasteric reflexes. Babinski's sign may be positive unilaterally or bilaterally and ankle clonus may be

present. A working knowledge of the segmental distribution of the spinal nerves is of great assistance in identifying the site of the tumor. The disclosure of a "sensory level," below which there is anesthesia or hypesthesia is immediately important in locating the exact position of the tumor in relation to the length of the cord. Acute flexion of the head on the chest or bilateral compression of the jugular veins as described by Jones and Naffziger[2] may reproduce the pain caused by a spinal cord tumor.

Anteroposterior and lateral roentgenograms of the spine should be taken in every case. Primary bone tumors and metastatic tumors of the vertebrae may produce characteristic changes in the films. Increased width of the spinal canal, narrowing of the pedicles and laminae, and enlargement of an intervertebral foramen may reveal the site of an intraspinal tumor.

The most important aids to diagnosis are lumbar puncture, Queckenstedt's test, and examination of the cerebrospinal fluid. Lumbar puncture is performed usually between the third and fourth lumbar vertebrae with the patient lying on his side. When fluid appears, its color is noted and a glass manometer is attached to the end of the needle. The height of the column of fluid in the manometer is recorded in millimeters as the initial pressure. The patient should be completely relaxed and free from apprehension during this measurement. The fluid below a cord tumor is often yellow or faintly straw-colored (xanthochromia). The arterial pulsations of the fluid in the manometer are observed. Below a tumor these pulsations are often minimal or absent. Queckenstedt's test is performed by compressing the jugular veins in the neck, either by hand or by application of a pneumatic pressure cuff. Normally, in the absence of spinal subarachnoid block, the increased intracranial pressure thus produced is immediately transmitted to the cerebrospinal fluid which promptly rises in the manometer. On release of jugular compression, the column of fluid falls to its initial level. In the presence of a tumor obstructing the free flow of cerebrospinal fluid through the spinal subarachnoid space, Queckenstedt's test results in no rise or a slow, incomplete rise of the fluid in the manometer. A complete or partial spinal subarachnoid block, as shown by this test, occurs in more than 90 per cent of cases of spinal cord tumor. A "dry tap," a "bloody tap," or severe pain may occur in the presence of a tumor of the cauda equina. When obtainable, 5 cc. of fluid are removed for examination. Lumbar puncture may be followed by an increase in all the symptoms and signs of the tumor. Examination then may show a definite "sensory level" which previously was not clear.

A determination of the cell count, of globulin and total protein content, and the Wassermann reaction of the cerebrospinal fluid are made.

The cell count is rarely abnormal and the amount of globulin and total protein is almost always increased in cases of spinal cord tumor.

When the level of the tumor cannot be determined accurately by neurologic examination, it is helpful to inject 1 cc. of heavy lipiodol into the cisterna magna. Then, with the patient lying on a tilting table, under the fluoroscope, the descent of the oil is observed. The lipiodol is completely or partially blocked by a tumor obstructing the spinal subarachnoid space. At times, the major portion of the mass of oil may be arrested above a tumor and a thin stream of oil may be seen to "squeeze" past the tumor very slowly. Roentgen films of the site of obstruction are made so that the laminectomy may be planned to expose the tumor with accuracy.

In addition to the previously mentioned conditions which may simulate "root pain," many diseases of the spinal cord must be considered in differential diagnosis. Among these are the following: tabes dorsalis, multiple sclerosis, subacute combined degeneration of the cord associated with pernicious anemia, deficiency disease, syringomyelia, arteriosclerosis of the spinal arteries, amyotrophic lateral sclerosis, involvement of the cord in Hodgkin's disease, cord compression in Pott's disease of the spine, and extradural pyogenic abscess.

The following case reports may help to give a more graphic picture of the clinical manifestations of spinal cord tumor:

Case 1: A healthy young man, 23 years of age, was referred to the Clinic February 19, 1935, by Dr. Macy Ginsburg, of Canton, Ohio, with a chief complaint of "backache." During the previous two years, the patient had had almost continuous lumbar backache, which had become more severe during the past five months. Occasionally, the pain radiated down the back of the left thigh and into the left calf. The lower back was quite stiff and could not be moved without severe pain. The patient was unable to cough or sneeze without experiencing severe pain. There was no numbness, loss of control of the sphincter, loss of potency, or weakness of the legs. No history of trauma could be elicited.

Neurological examination revealed marked limitation of all movements in the lower back, increased lumbar lordosis, severe pain and restricted movement on straight leg raising, no weakness or atrophy of the legs, sluggish abdominal reflexes, active cremasteric and anal reflexes, hyperesthesia to pin-prick over the lower lumbar area and over the buttocks. There was no anesthesia. The patellar and Achilles reflexes were active and there was a questionable Babinski's sign bilaterally.

In the Orthopedic Department, a tentative diagnosis of early ankylosing arthritis of the lumbar spine and sacro-iliac joints was made. Certainly the clinical picture thus far warranted such a diagnosis. The diagnostic importance of lumbar puncture in such cases, however, was not forgotten. This procedure was carried out with some difficulty between the third and fourth lumbar vertebrae, and yellow, nonpulsating fluid was obtained at a pressure of 100 mm. of water (normal). Queckenstedt's test revealed a partial spinal

subarachnoid block and, after withdrawal of 6 cc. of fluid, the pressure fell to zero. The fluid coagulated on standing, thus signifying a high protein content. Examination of the fluid revealed 1 cell, globulin ++++, total protein 2000 mg. per 100 cc., negative Wassermann reaction, and negative colloidal gold curve.

A diagnosis of spinal cord tumor was made and, in order to locate it with accuracy, 1 cc. of lipiodol was introduced into the cisterna magna. Roentgen studies showed that its descent was arrested at the upper level of the body of the third lumbar vertebra.

On February 25, 1935, laminectomy of the second, third, and fourth lumbar vertebrae was performed and a neurofibroma of the cauda equina was found and removed (Fig. 1). The tumor was encapsulated and somewhat dumbbell

FIGURE 1: Cut surface of neurofibroma of the cauda equina.

shaped, with a moderate extradural extension through the intervertebral foramen between the fourth and fifth lumbar vertebrae on the left side.

After an uneventful recovery the patient was discharged from the hospital on the seventeenth day after operation. He was last observed on June 29, 1937, two years and four months following removal of the tumor. At that time, he had no pain in the back or legs and no difficulty in the movements of his spine. He had been working steadily. Examination revealed no neurological abnormality.

In this case a *tumor of the cauda equina simulated clinically an arthritic condition of the lumbar spine and sacro-iliac joints.* Lumbar puncture was the deciding factor in arriving at the true diagnosis. *In the following case, a spinal cord tumor simulated clinically a degenerative lesion of the cord,* and again lumbar puncture indicated the true nature of the condition.

Case 2: A 48 year old repair man was referred to the Clinic on November 13, 1933, by Dr. C. La Mont of Canton, Ohio. He complained chiefly of "numbness, burning, and drawing in the right leg." The lower back had been injured in an automobile accident in 1928. Roentgen films taken at that time showed no fracture of the spine. There was no paralysis. Two weeks later the patient returned to work. One year after the accident, he first noticed severe pain in the upper right lumbar region while coughing or while riding in his car over rough roads. In 1930, he began to have a burning sensation and numbness of the sole of the right foot and this gradually extended up to the right calf and to the anterior aspect of the right thigh during the next three years. Occasional, involuntary jerking movements of the right leg had occurred during the past six months, and the patient had walked with a limp, stumbling with the right foot during the past two years. He was unable to identify the position of the right foot without seeing it. During the month prior to examination at the Clinic, a sensation of numbness had developed in the sole of the left foot. There had been occasional incontinence of loose stools, but no incontinence of urine. Potency was good.

Neurological examination revealed diminished perception of all forms of sensation from the knees to the toes in both legs and feet. The right leg was weak and slightly spastic. Patellar and Achilles reflexes were hyperactive on both sides and Babinski's sign was positive bilaterally, but there was no clonus. The Romberg test gave a positive reaction. The gait was somewhat spastic.

In differential diagnosis the following conditions required consideration: multiple sclerosis, spinal cord tumor, subacute combined degeneration of the cord associated with pernicious anemia, and syphilis.

Routine blood examinations, including a Wassermann reaction, gave negative findings.

Roentgen examination of the spine was negative except for hypertrophic changes.

Lumbar puncture obtained clear, slightly yellow fluid at an initial pressure of 140 mm. of water (normal). There was a complete spinal subarachnoid block as shown by Queckenstedt's test. Examination of the cerebrospinal fluid thus obtained revealed 1 cell, a trace of globulin, total protein 200 mg. per 100 cc., negative Wassermann reaction, and negative colloidal gold curve.

It was then possible to make a diagnosis of spinal cord tumor by correlating the history, the neurological examination, the spinal subarachnoid block, and the high protein content of the cerebrospinal fluid. Inasmuch as the neurological examination failed to reveal a definite "sensory level" by which the tumor could be accurately localized, it was necessary to inject 1 cc. of lipiodol into the cisterna magna and then with the fluoroscope to follow its descent in the spinal canal. The lipiodol was arrested at the level of the ninth thoracic vertebra.

On November 23, 1933, laminectomy of the eighth, ninth, tenth, and eleventh thoracic vertebrae was carried out and a neurofibroma of a spinal nerve was found. The tumor was intradural and extramedullary, encapsulated, about 2 cm. long, compressing the right posterolateral aspect of the cord just beneath the lamina of the ninth thoracic vertebra. It was removed without great difficulty. Convalescence was uneventful except for a mild urinary infection which lasted for five days. The patient was in good condition when he was discharged from the hospital on the twenty-second postoperative day. At that

time he was walking without difficulty, sensation in the legs had returned to normal, and Babinski's sign had disappeared on both sides.

Two months after operation, the patient was working every day and walking without difficulty. Numbness had entirely disappeared and pain had not recurred. Neurological examination showed no abnormality five months after operation. On April 24, 1935, the patient again reported to the Clinic and expressed his good spirits and the normal motor function of his lower extremities by performing an intricate "tap dance" on the floor of the office. He last reported by mail on September 1, 1937, and stated that he was "feeling fine."

In the presence of a rapidly developing compression of the spinal cord, whether by fracture, by hemorrhage, or by tumor, the prognosis for return of normal motor function is usually poor. Such a condition existed in the following case which was the result of a solitary plasma cell myeloma of the spine. This type of lesion is somewhat rare and has been reported previously by Klemme[3], Denker and Brock[4], and Wakeley[5].

Case 3: On July 4, 1936, a 42 year old man was seen in consultation with Dr. C. H. Hodgkinson and Dr. S. G. Foster at Oil City, Pennsylvania. The patient had enjoyed good general health until one month previously when he began to notice an intermittent, aching pain between the shoulder blades. One week prior to consultation, there had been a rapid development of weakness and numbness in both legs, and the patient was confined to bed because of inability to stand or walk. For one week, he had been unable to defecate and was obliged to resort to an enema.

Neurological examination revealed complete spastic paralysis of both legs, complete anesthesia caudal to the fifth rib, absent abdominal and cremasteric reflexes, and hyperactive patellar reflexes.

Lumbar puncture obtained clear, yellow fluid at an initial pressure of 90 mm. of water. Arterial pulsations were absent. There was a complete spinal subarachnoid block as shown by Queckenstedt's test. Examination of the fluid showed no cells, a marked trace of globulin, total protein 325 mg. per 100 cc., negative Wassermann reaction, and negative colloidal gold curve.

Roentgen examination of the spine in the lateral view showed erosion of the spinous process and laminae of the fourth thoracic vertebra (Fig. 2).

A diagnosis was made of neoplasm compressing the spinal cord at the level of the fourth thoracic vertebra. In this case it was possible to localize the level of the tumor exactly by the neurological examination and by the roentgen films of the spine so that lipiodol studies were not necessary.

At operation July 7, 1936, a soft, reddish-gray tumor mass was found to involve the spinous process and laminae of the fourth thoracic vertebra. The laminae had been completely destroyed and replaced by tumor tissue. The mass extended laterally to invade the muscles on each side. The tumor was removed as completely as possible and was found to be entirely extradural. A cleavage plane existed between the dura and the overlying tumor. The cord had been markedly compressed and, after removal of the tumor, the dura pulsated normally throughout the area of the exposure. The cavity from which the tumor was removed appeared to be as large as a golf ball. Where the neoplasm invaded the muscles on each side, it did not seem to be encapsulated. The cord was well decompressed and the wound was closed.

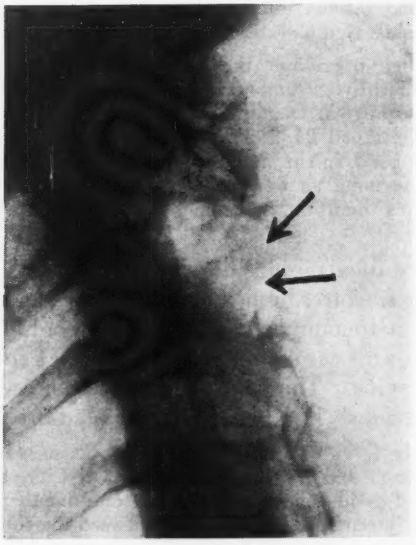

FIGURE 2: Lateral roentgenogram of spine showing erosion of spinous process and laminae of the fourth thoracic vertebra by plasma cell myeloma.

Microscopic examination of the tumor tissue revealed a very cellular structure of uniform type. The predominant cell was that of a plasma cell myeloma. The tumor was well vascularized and contained very little fibrous stroma or necrosis. The pathological diagnosis was plasma cell myeloma of the spine (Fig. 3).

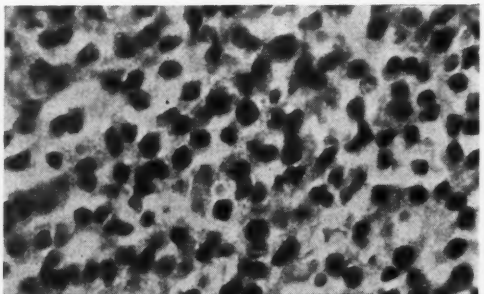

FIGURE 3: Photomicrograph of plasma cell myeloma (x 600).

Because of the nature of the tumor, the patient received a course of roentgen therapy before he left the hospital. Within a week following operation, he regained normal sensation in the lower half of the body. Motor function, as

usual in cases of rapid compression of the cord, failed to show improvement parallel to that of sensory function. The patient was able to flex and extend his legs slightly before leaving the hospital on the twenty-sixth day after operation.

When the nature of the tumor was known, a search for Bence-Jones protein in the urine was made on several occasions, but none was found.

The patient returned to the Clinic for further roentgen therapy in October 1936 and in March 1937. He was last seen at the Clinic on June 21, 1937, at which time he was able to walk slowly with the aid of crutches. Both legs were still spastic, but the left leg showed marked improvement in voluntary motion. Babinski's sign persisted on both sides. Sensation was normal. The patient had normal control of vesical and rectal function.

He has been asked to return every four months for observation and further roentgen therapy, if indicated. Thus far there has been no evidence of myeloma involving any bones of the body other than the fourth thoracic vertebra and there has been no evidence of local recurrence.

Treatment

At the present time the primary treatment of spinal cord tumors is surgical exposure, removal of the growth if possible, and decompression of the cord. A good prognosis attends the removal of benign extramedullary neoplasms, unless compression of the cord has been prolonged to the stage of permanent damage to the cord. The treatment of gliomas of the cord and of tumors causing rapid compression of the cord offers much less hope of good results. Since it is rarely possible to make a preoperative diagnosis of the type of tumor, surgical exploration is warranted in every case of tumor involving the spinal cord, unless there are other general contraindications to major surgery. If radiosensitive tumors are encountered, roentgen therapy, of course, offers the best opportunity for improvement in the condition of the patient.

In conclusion, it may be worth while to emphasize again the importance of considering the possibility of spinal cord tumor in the differential diagnosis of certain conditions characterized by pain, by changes in motor function, or by changes in sensory function. In this regard, the inestimable value of lumbar puncture and Queckenstedt's test must not be forgotten.

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THE MECHANISM OF ANEMIA*

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Anemia is a reduction below normal of the capacity of the blood to transport the oxygen necessary for all animal life. The body tissues must be supplied with many times as much oxygen as can be carried in physical solution in the plasma. The hemoglobin normally present (15 to 16 gm. per 100 c.c. of blood) increases one hundred times the power of the blood to transport oxygen by carrying it in chemical combination. This amount of hemoglobin in solution in the circulating blood would greatly increase the osmotic pressure of the plasma beyond that of the surrounding tissues and so dehydrate the tissues. Hemoglobin in a red cell is outside the plasma, does not affect the osmotic pressure, and yet functions efficiently as an oxygen carrier since absorption and release of oxygen is as efficient as if the hemoglobin were in solution in the plasma. The red cell is thus simply a container[1] for the necessary hemoglobin and functions as a cup on an endless-chain conveyor. It is normally filled with hemoglobin and is constantly making round trips from the lungs to the tissues. This conception of the function of the red cell applied to the different laboratory types of anemia is illustrated in Fig. 1. In addition to thinking of the red cell as a cup on an endless-

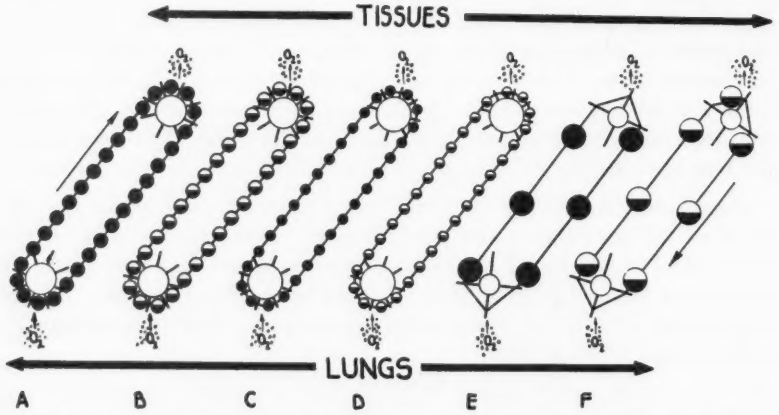

FIG. 1.—Schematic illustration of red cells functioning as units (cups) on an endless-chain conveyor. *A*, Normal red cells. *B*, Red cells of normal size partly filled with hemoglobin (normocytic, hypochromic anemia). *C*, Small red cells completely filled with hemoglobin (microcytic, hypochromic anemia). *D*, Small cells, partly filled with hemoglobin (microcytic, hypochromic anemia). *E*, Large cells, completely filled with hemoglobin (macrocytic, hyperchromic anemia). *F*, Large cells containing a normal amount of hemoglobin (macrocytic, normochromic anemia).

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chain conveyor, we should also visualize the total mass of circulating red cells as a vessel containing hemoglobin. The size of this vessel varies enormously in blood dyscrasias affecting the red cell as illustrated in Fig. 2.

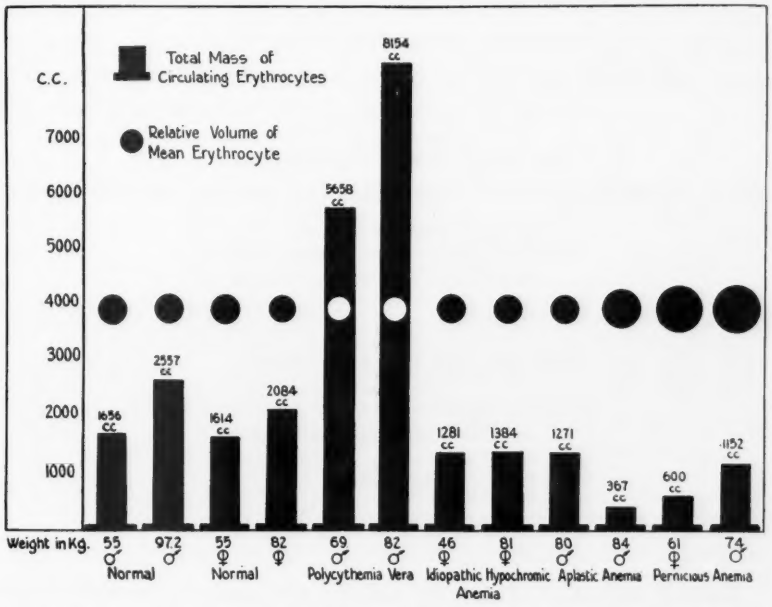
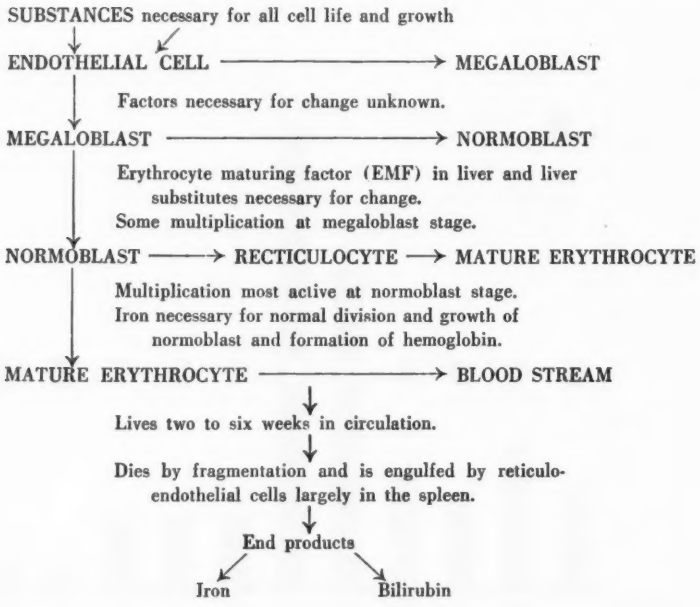


FIG. 2.—Variation in total mass of circulating red cells in various conditions. The circle indicates the relative volume of the unit of mass (the red cell) in each instance.

The problem of anemia is primarily concerned with hemoglobin and its carrier, the red cell. The span of life of a red cell averages thirty days. About a trillion red cells are formed and destroyed each day since the number normally in the circulation shows little variation. The life history of the erythrocyte is shown in Table I. To form red cells, nonspecific substances necessary for building all cells are needed. These are protein, fat, carbohydrate, water, vitamins, and mineral salts. Two specific substances are also required, the iron necessary for hemoglobin formation and the substance supplied by liver and liver substitutes necessary for the maturation of red cells. To evaluate an anemia, we must understand red cell formation in the marrow, know the level of circulating elements, and visualize the rate of red cell and hemoglobin destruction.

TABLE I

LIFE HISTORY OF THE ERYTHROCYTE


SUBSTANCES necessary for all cell life and growth
ENDOTHELIAL CELL
MEGALOBLAST
Factors necessary for change unknown.
MEGALOBLAST
NORMOBLAST
Erythrocyte maturing factor (EMF) in liver and liver substitutes necessary for change.
Some multiplication at megaloblast stage.
NORMOBLAST
RECTICULOCYTE
MATURE ERYTHROCYTE
Multiplication most active at normoblast stage.
Iron necessary for normal division and growth of normoblast and formation of hemoglobin.
MATURE ERYTHROCYTE
BLOOD STREAM
Lives two to six weeks in circulation.
Dies by fragmentation and is engulfed by reticulo-endothelial cells largely in the spleen.
End products
Iron
Bilirubin

Certain indicators of red cell activity are necessary to evaluate the formation, circulation, and destruction of red cells. The red cell count and the hemoglobin content record only the balance between red cell formation and red cell destruction. Young red cells have the property of staining with certain dyes before they are fully matured. The number of reticulocytes or young cells which take this stain is an index of the rate of production of red cells ready to function in the blood stream or at least the rate of delivery of such cells from the marrow. The marrow may be hyperplastic or hyperactive with a low reticulocyte count in the circulation if the delivery of cells from the marrow is impaired. If the reticulocyte count in the circulation is high, the marrow is necessarily hyperplastic; if below normal the marrow may be aplastic, hypoplastic, or hyperplastic.

When a red cell is destroyed, hemoglobin is set free, iron is split off from the hemoglobin molecule, and bilirubin is formed as the end product of the pigment metabolism. Bilirubin so formed is adsorbed

by protein and is not easily excreted by the kidney. The capacity of the liver cells to excrete bilirubin so formed is also quickly exceeded, so an excessive destruction of red cells and hemoglobin is soon reflected in an increased bile pigment content of the plasma. In the absence of biliary obstruction and liver disease, the amount of bilirubin present in the plasma is an indicator of the rate of red cell and hemoglobin destruction. A correlation of the bilirubin content of the plasma and the reticulocyte level is shown in Table II.

TABLE II

RELATION OF BLOOD FORMATION AND DESTRUCTION TO BILIRUBIN AND RETICULOCYTE LEVEL

BILIRUBIN CONTENT (ICTERUS INDEX)	RECTICULOCYTE COUNT		
	INCREASED (OVER 1.5%)	NORMAL (0.5-1.5%)	DECREASED (UNDER 0.5%)
Increased (over 6 units)	Increased blood destruction with active bone marrow	Increased destruction without good marrow response	Increased destruction with inactive bone marrow or impaired delivery of red cells
Normal (4-6 units)	Active bone marrow without excessive destruction	Decreased marrow without excessive destruction of red cells	Decreased formation or impaired delivery of red cells without excessive destruction.
Decreased (under 4 units)	Decreased destruction of hemoglobin due to iron deficiency; active cell formation in marrow	Decreased destruction of hemoglobin. Decreased formation of hemoglobin; normal cell formation in marrow	Decreased destruction of hemoglobin. Decreased formation of hemoglobin. Decreased cell formation in marrow or impaired delivery of cells

If all elements necessary for red cell formation are deficient, the marrow cannot make the normal number of cells at the normal rate. The marrow functions at a low rate of speed but such cells as are delivered into the circulation are usually normal. The two specific elements, iron and erythrocyte maturing factor (EMF), are necessary if the marrow is to make a normal cell with a normal complement of hemoglobin. As the red cells develop in the bone marrow, they multiply actively at the megaloblast stage but are not ready for delivery from the marrow until completed by a substance formed by the interaction of a secretion of the stomach (the intrinsic factor of Castle) on food elements (the extrinsic factor of Castle) and stored in the liver. This substance has been designated by many names, as "liver principle," the "antianemic principle of Castle," the "pernicious anemia principle," and "anti-megalocyte principle." Its fundamental action is to mature the red cell, or prepare it for emergence from the marrow, so we have designated it

erythrocyte maturing factor (EMF). Since it is always necessary to know, in studying an anemia, whether there is a sufficient supply of this essential factor, we must have some indicator of its lack. The cell to which this substance (EMF) is supplied becomes smaller so a decrease in volume of the cell is characteristic of the maturation effected by the erythrocyte maturing factor and a macrocytosis is indicative of its lack. While a macrocytosis is usually an indicator of a deficiency of the erythrocyte maturing factor (EMF), cells of increased size may be due to other causes. A hyperplastic marrow, overactive in response to a great demand for red cells, may deliver red cells larger than normal. These are large because of rapid removal from the marrow before maturation is complete rather than a lack of erythrocyte maturing substance (EMF). Thus the hyperplastic marrow in response to rapid destruction of red cells in phenylhydrazine poisoning or in spherocytic jaundice may deliver macrocytic cells. A chronic hyperplasia of marrow in response to increased cell loss usually leads in time, however, to the formation of cells smaller than normal. Iron is the second specific element necessary for normal red cell formation. Without iron, hemoglobin cannot be formed. It is most probable also that iron stimulates the growth and multiplication of red cells at the normoblast stage where division is most active. With a decrease in the normal amount of hemoglobin in the blood, there is first a decrease in the concentration of hemoglobin in the red cells or decreased color index. Since there is no value in having red cell stroma without hemoglobin to fill it, if the color index continues low, the cells become smaller and the volume index decreases. The hypochromia shown by the lessened color index and volume index is a measure of the lack of iron.

Thus we have accurate indicators to show the balance between red cell formation and cell destruction (the red cell count and hemoglobin content), the rate of destruction of red cells (the icterus index), the rate of regeneration or delivery of red cells (the reticulocyte count), the lack of the erythrocyte maturing factor or EMF (macrocytosis), and a deficiency of iron (hypochromia and microcytosis) as tabulated in Table III. I have described elsewhere the technic of the blood exami-

TABLE III

MEASURES OF RED CELL ACTIVITY

FACTOR	INDICATOR
Balance of red cell and hemoglobin formation and destruction	Red cell count and hemoglobin content
Rate of destruction of red cells	Level of bile pigment in plasma
Rate of regeneration of red cells	Level of reticulocytes in circulation
Deficiency of iron	Hypochromia and microcytosis of red cells
Deficiency of erythrocyte maturing factor (EMF)	Macrocytosis of red cells

nation to supply such data.[2] A careful laboratory study is first necessary in every anemia to furnish the data outlined above. From the laboratory examination the anemia is classified on the basis of the number, size, and hemoglobin content of the mean red cell.[3] These studies are illustrated in Fig. 3. The relation of the blood findings to red cell formation and destruction is shown in Table IV.

TABLE IV

RELATION OF BLOOD FINDINGS TO RED CELL FORMATION AND DESTRUCTION

Active bone marrow	Increased number of reticulocytes, basophilia, nucleation. Slight increase in mean erythrocyte volume if reticulocytosis is marked. Often an increase in leucocytes and platelets unless destruction is more active than normal. The number of cells is increased
Inactive bone marrow	Decrease or absence of reticulocytes, basophilia and nucleation. If blood destruction is normal or increased, the cell count decreases
Increased red cell and hemoglobin destruction	Increase in bilirubin content of plasma; decrease in number of cells unless compensated for by increased marrow activity
Decreased hemoglobin destruction	Decrease in bilirubin content of plasma
Deficiency in erythrocyte maturing factor (pernicious anemia)	Anemia with increase in mean erythrocyte volume (increased volume index)
Deficiency in iron (iron deficiency anemia; chronic hemorrhagic anemia)	Anemia with hypochromia of red cells (decreased color index); microcytosis (decreased volume index); if hypochromia continues
Hemolytic anemia	Anemia with increased icterus index; reticulocytosis if marrow responds to increased need
Anemia due to decrease in amount or activity of marrow (aplastic or hypoplastic anemia)	Anemia with cells of normal size and hemoglobin content; decrease in reticulocytes

Since an anemia represents a loss of balance between red blood cell formation and destruction, an anemia can result only from increased blood loss without a compensating increase in blood formation, by decreased formation with a normal or accelerated blood loss, or by a combination of increased blood loss and decreased formation. A clinical classification of anemia on the basis of method of production with the more important clinical causes is given in Table V. In every anemia it is necessary to make both a laboratory and clinical classification.

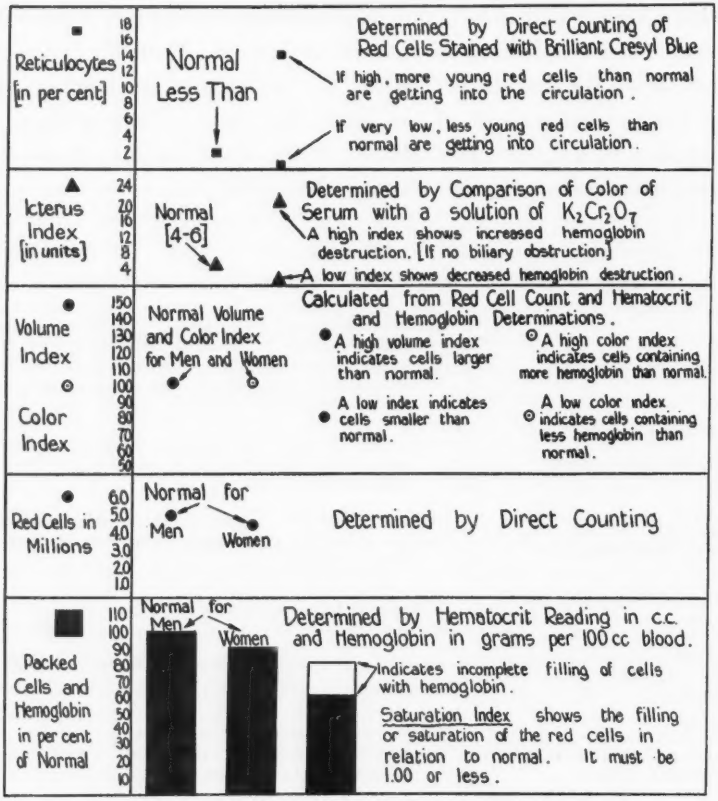

Reticulocytes [in per cent]
18 16 14 12 10 8 6 4 2
Normal Less Than
Determined by Direct Counting of Red Cells Stained with Brilliant Cresyl Blue
If high, more young red cells than normal are getting into the circulation.
If very low, less young red cells than normal are getting into circulation.
Icterus Index [in units]
24 20 16 12 8 4
Normal [4-6]
Determined by Comparison of Color of Serum with a solution of $K_2Cr_2O_7$
A high index shows increased hemoglobin destruction. [If no biliary obstruction]
A low index shows decreased hemoglobin destruction.
Volume Index
Color Index
150 140 130 120 110 100 90 80 70 60 50
Normal Volume and Color Index for Men and Women
Calculated from Red Cell Count and Hematocrit and Hemoglobin Determinations.
A high volume index indicates cells larger than normal.
A low index indicates cells smaller than normal.
A high color index indicates cells containing more hemoglobin than normal.
A low color index indicates cells containing less hemoglobin than normal.
Red Cells in Millions
6.0 5.0 4.0 3.0 2.0 1.0
Normal for Men Women
Determined by Direct Counting
Packed Cells and Hemoglobin in per cent of Normal
110 100 90 80 70 60 50 40 30 20 10
Normal for Men Women
Determined by Hematocrit Reading in c.c. and Hemoglobin in grams per 100 cc blood.
Indicates incomplete filling of cells with hemoglobin.
Saturation Index shows the filling or saturation of the red cells in relation to normal. It must be 1.00 or less.

FIG. 3.—Study of blood and interpretation of findings in anemia.

TABLE V

CLINICAL CLASSIFICATION OF ANEMIA

I. Increased blood loss
   1. Mechanical loss from hemorrhage
   2. Accelerated red cell destruction by:
      a. Hemolytic agents (as phenylhydrazine or bacterial toxin)
      b. Rapid red cell removal from an abnormality of cell shape (as congenital hemolytic icterus), overactivity of reticulo-endothelial system, or defect in cell structure

II. Decreased blood formation
   1. Quantitative decrease in red marrow from aplasia as in benzol poisoning, or crowding out of erythrogenic tissue as in leucemia or myeloma
   2. Quantitative depression of marrow activity as by malignancy, hypometabolism, chronic toxemia such as nephritis or cachexia
   3. Qualitative decrease in marrow activity from deficiency of specific substances necessary for normal marrow activity
      a. Deficiency in supply, absorption, or use of erythrocyte maturing factor (EMF) as in pernicious anemia or sprue
      b. Deficiency in supply, absorption, or use of iron as in chronic hemorrhage, dietary lack, and idiopathic hypochromic anemia

MECHANISM OF ANEMIA

With a careful study of the blood and determination of each of the indicators of red cell activity, a clinical study of the patient and a clinical classification of the anemia, the different types of anemia can be visualized by means of diagrams. In each diagram, the blood is depicted in relation to the three phases of the red cell, viz., (1) formation, (2) circulation, and (3) destruction. The fundamental fault in the production of the anemia is apparent in such a diagram, so the point of attack in treatment is evident.

In Fig. 4, the normal cell is shown in relation to formation, circulation, and destruction. The bone marrow is thought of as a gristmill with three hoppers supplying materials for making red cells. One hopper supplies the nonspecific elements and the other two the specific elements. Normally, the hoppers are full. The level in the mill indicates the relative fullness of the bone marrow. To maintain the normal balance between formation and destruction, nearly one trillion cells and 25 gm. hemoglobin must be formed daily. In the circle showing the normal circulation are 100 red cells with one reticulocyte. The cells are of normal size and hemoglobin content. The normal findings are shown below the circle. Old red cells are taken out by the reticuloendothelial cells, largely those of the spleen. If the blood count remains constant as it normally does, the same number must be taken out as are delivered to the blood stream by the marrow. As the hemoglobin is destroyed, iron is split off. Some of the iron is excreted but the larger part (85 per cent) is returned to the marrow to be used again. The end product of hemoglobin destruction is bilirubin which is excreted by the liver. The normal amount of bile pigment and iron formed is indicated by the level of these substances in the containers in which they are received. We think of the mill as functioning at a constant rate of speed so as to supply the same number of cells with the same hemoglobin content as are destroyed each day. The normal mean elapsed time between the beginning of formation of the cell and the ultimate disposal of it is thirty days.

Every anemia can be illustrated by such a diagram. In Fig. 5 is shown the red cell mechanism immediately after a large hemorrhage from the uterus. The cells remaining in the circulation are normal and the process of formation and destruction is unaltered. This state persists for only a short time, however, after the hemorrhage, when there is increased activity of the marrow to compensate for the blood lost. The icterus index falls (2 units) and the amount of bilirubin and iron set

free decreases, and the picture is now one of an iron deficiency anemia, shown in Fig. 6, where there is a defect in the supply of iron to the

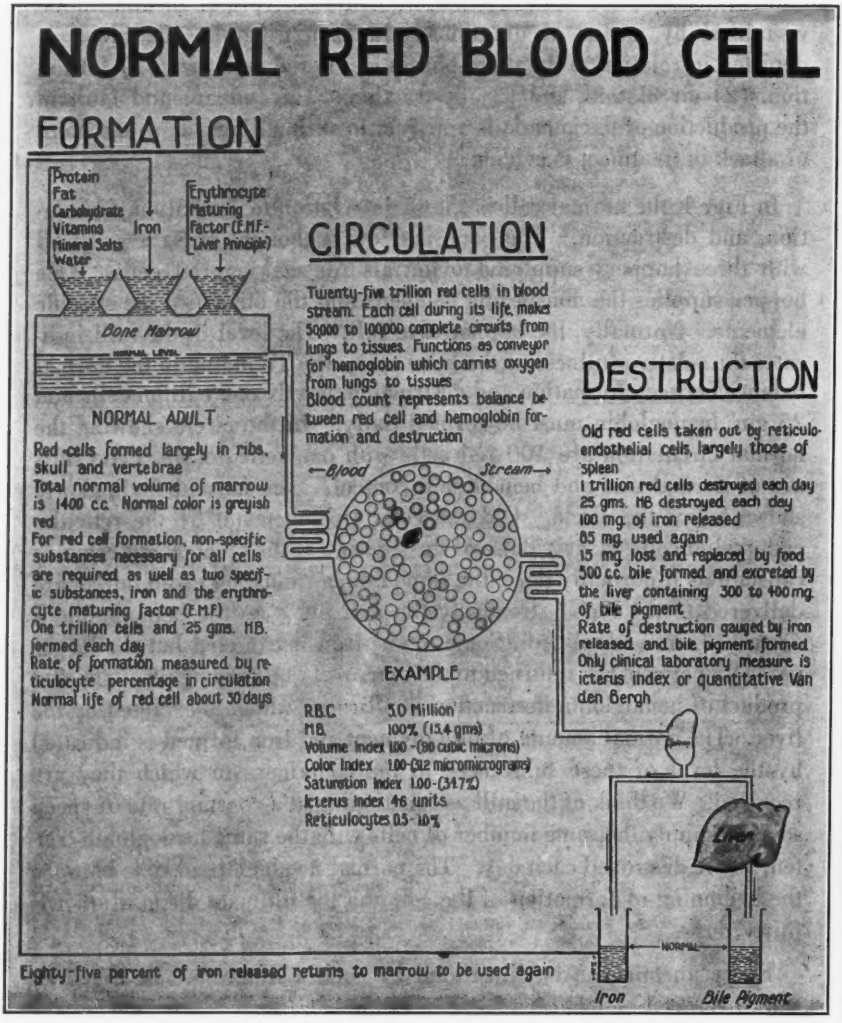

NORMAL RED BLOOD CELL
FORMATION
Protein
Fat
Carbohydrate
Vitamins
Mineral Salts
Water
Iron
Erythrocyte Maturing Factor (E.M.F.-Liver Principle)
Bone Marrow
NORMAL LEVEL
NORMAL ADULT
Red cells formed largely in ribs, skull and vertebrae
Total normal volume of marrow is 1400 c.c. Normal color is greyish red
For red cell formation, non-specific substances necessary for all cells are required as well as two specific substances, iron and the erythrocyte maturing factor (E.M.F.)
One trillion cells and 25 gms. HB. formed each day
Rate of formation measured by reticulocyte percentage in circulation
Normal life of red cell about 30 days
CIRCULATION
Twenty-five trillion red cells in blood stream. Each cell during its life makes 50,000 to 100,000 complete circuits from lungs to tissues. Functions as conveyor for hemoglobin which carries oxygen from lungs to tissues
Blood count represents balance between red cell and hemoglobin formation and destruction
←Blood Stream→
EXAMPLE
R.B.C. 5.0 Million
HB. 100% (13.4 gms)
Volume Index 1.00 - (90 cubic microns)
Color Index 1.00 - (31.2 micromicrograms)
Saturation Index 1.00 - (34.7%)
Icterus Index 4.6 units
Reticulocytes 0.5 - 1.0%
DESTRUCTION
Old red cells taken out by reticulo-endothelial cells, largely those of spleen
1 trillion red cells destroyed each day
25 gms. HB destroyed each day
100 mg. of iron released
85 mg. used again
15 mg. lost and replaced by food
300 c.c. bile formed and excreted by the liver containing 300 to 400 mg. of bile pigment
Rate of destruction gauged by iron released and bile pigment formed
Only clinical laboratory measure is icterus index or quantitative Van den Bergh
Liver
NORMAL
Eighty-five percent of iron released returns to marrow to be used again
Iron
Bile Pigment

FIG. 4.—Normal red cell physiology.

marrow with the result that the cells are small (volume index 0.067) and have a decreased hemoglobin content (color index 0.4). The therapeutic indication is to stop the blood loss and supply an adequate amount of iron.

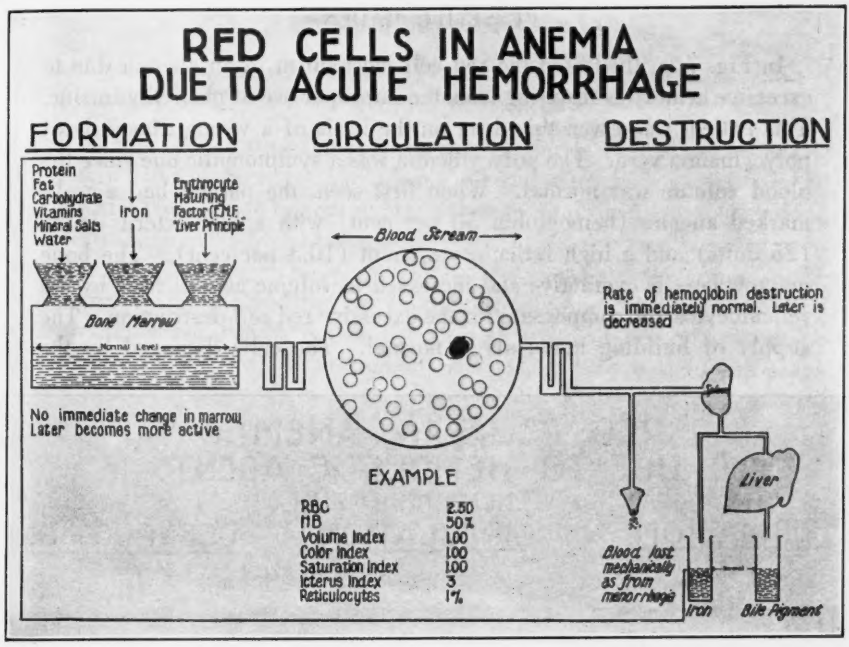


FIG. 5.—Physiology of red cells after an acute hemorrhage.

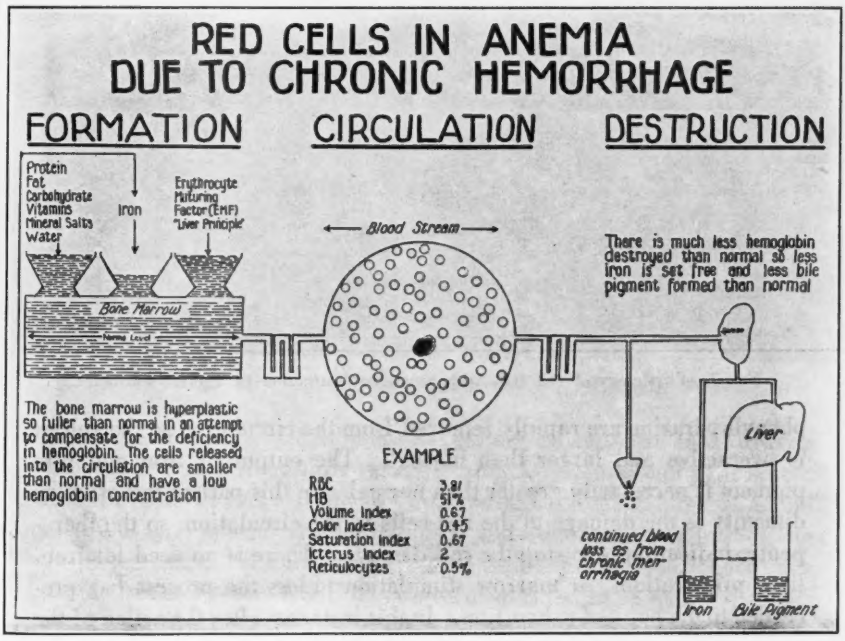


FIG. 6.—Physiology of red cells after a chronic hemorrhage.

In Fig. 7 is illustrated the red cell mechanism in an anemia due to excessive hemolysis resulting from the improper use of phenylhydrazine. This patient was given this drug on the basis of a wrong diagnosis of polycythemia vera. The polycythemia was a symptomatic one since the blood volume was normal. When first seen, the patient had a well-marked anemia (hemoglobin 58 per cent) with a high icterus index (25 units) and a high reticulocyte count (10.3 per cent). The bone marrow here is overactive and increased in volume as indicated by the reticulocytosis to compensate for the excessive red cell destruction. The supply of building materials is normal. The cells damaged by the

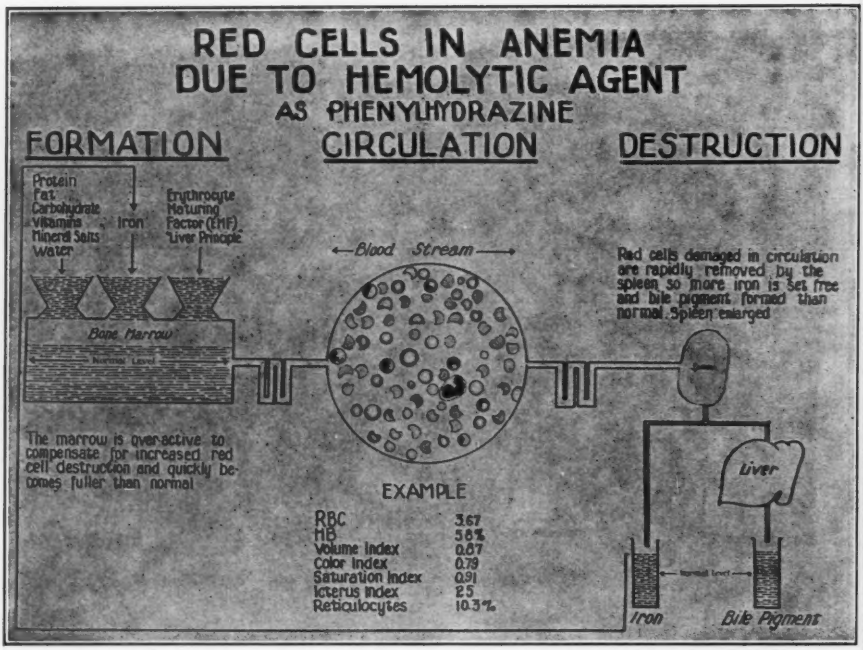


FIG. 7.—Physiology of red cells with excessive destruction by a toxic substance.

phenylhydrazine are rapidly removed from the circulation so the spleen is overactive and larger than normal. The output of iron and bile pigment is necessarily greater than normal. In this patient the primary difficulty is the damage to the red cells in the circulation, so the therapeutic indication is to stop the cell damage. There is no need for iron, liver preparations, or marrow stimulation unless the process has proceeded to the point of exhaustion. In this instance, after the action of the

drug was past, the spleen, icterus index, the reticulocyte count, the red cells, and hemoglobin all returned to normal.

In Fig. 8 is shown the red cell mechanism in congenital hemolytic icterus and spherocytic jaundice. This patient had a well-marked anemia with a high icterus index (15 units) indicating excessive blood destruction and a high recticulocyte count (10.8 per cent) showing good marrow response. The supply of building materials is ample so the hoppers are full and the active marrow is fuller than normal. The fundamental difficulty in this disease is an anatomic defect in the shape of the red cells which are spherocytic rather than normal biconcave

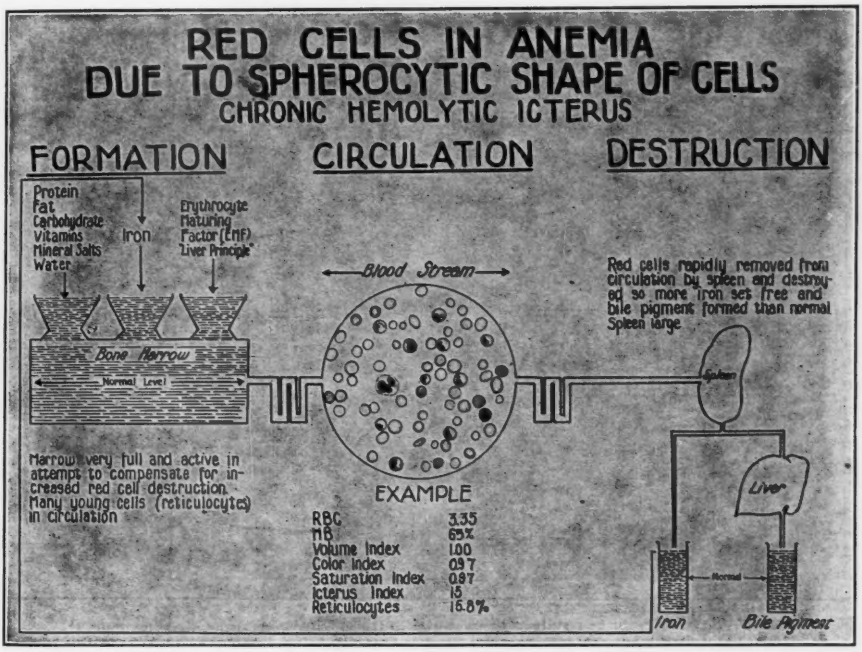


FIG. 8.—Physiology of red cells with excessive filtration by spleen (spherocytic anemia).

disks. As a result of this abnormal shape the cells are more fragile than normal[4] and are rapidly removed from the circulation by the spleen which is enlarged as a result of the increased activity. More iron and bilirubin than normal are poured out. Here the average length of life of the red cell is a few days instead of the usual thirty days. There is a rapid stream of cells from the site of origin, the bone marrow, to the place of destruction, the spleen. We cannot correct the anatomic defect

so the patient is treated by removing the filter. The abnormally shaped cells function normally if allowed to remain in the circulation. The anemia, reticulocytosis and jaundice all disappear after splenectomy, showing that the increased activity of the spleen is the cause of the anemia although the fundamental defect is in the bone marrow.

Sickle-cell anemia, shown in Fig. 9, has much in common with spherocytic anemia (congenital hemolytic icterus). Here also, there is a fundamental defect in the marrow with the delivery of cells of abnormal shape and probably with a greater tendency to

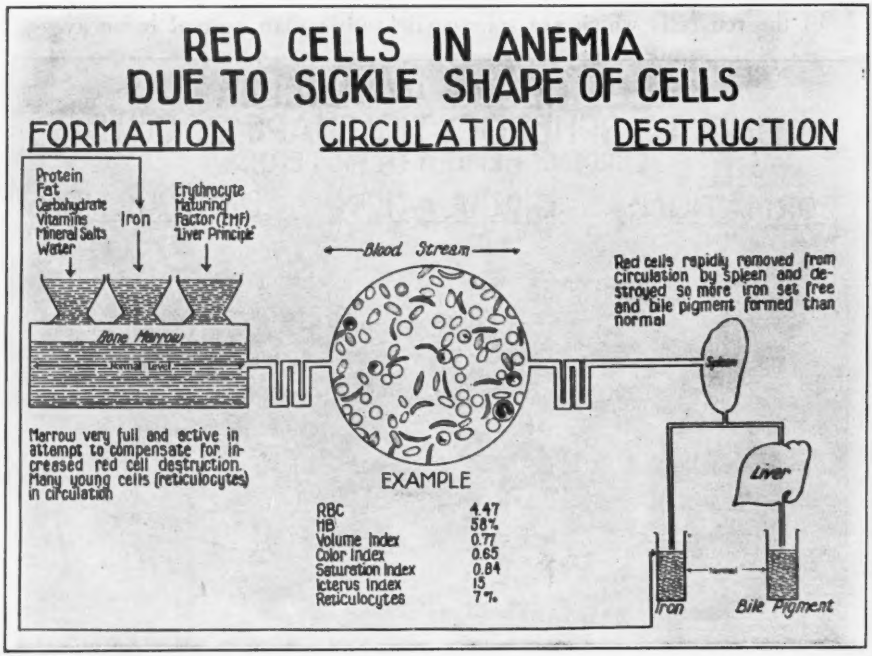


FIG. 9.—Physiology of red cells with excessive filtration by spleen (sickle-cell anemia).

fragment. The supply of building material is adequate, the marrow is overactive as shown by the reticulocytosis, and red cell destruction is excessive as shown by the increased icterus index. The spleen is enlarged at least early in the disease due to overactivity in removing excessive numbers of abnormal cells from the circulation. Splenectomy helps the anemia[5,6] but here the result differs from that seen in spherocytic anemia in that the patient continues to have some anemia after removal of the spleen. The increased cell destruction and formation also continue so the excessive activity of the spleen cannot be the

sole cause of the anemia. It is most probable that the red cells fragment more easily than normal and this fragmentation continues after splenectomy. There is no treatment for this phase of the disorder. Splenectomy removes only one factor in the anemia.

Fig. 10 illustrates the anemia due to marrow aplasia caused by the prolonged use of arsphenamine. The amount of functioning marrow tissue is decreased. In this instance the blood examination shows a marked anemia with cells of normal size (volume index, 0.97) and

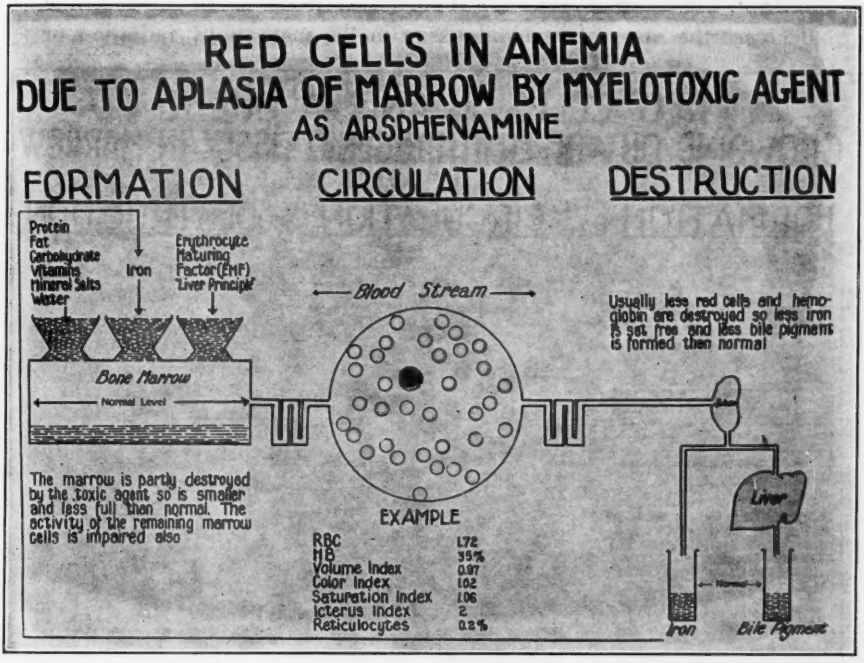


FIG. 10.—Physiology of red cells when formation of cells is decreased by aplasia of marrow.

hemoglobin content (color index, 1.02). The reticulocyte count is very low (0.2 per cent). The marrow is at a low level as indicated by the low red cell, white cell, reticulocyte, and platelet counts. The mill is greatly decreased in size although the supply of raw material is ample. There is less destruction of cells so the iron and bile pigment output are much below normal. It is apparent that this anemia can be treated only by measures designed to improve the size and function of the marrow. In this instance the marrow was permanently damaged and the patient finally died of the anemia.

Another type of anemia due to marrow deficiency is illustrated in Fig. 11. This is a myeloid leucemia with a marked anemia (hemoglobin 42 per cent). Here the marrow is full, but the increase in size is due to the hyperplasia of myeloid tissue at the expense of erythrogenic tissue, so there is a great decrease in red-cell-forming tissue and a consequent anemia. The spleen is also enlarged from infiltration of myeloid tissue and not from overactivity due to excessive cell destruction. There is less red cell destruction and so less iron is set free and less bile pigment formed. Here again, the indication for treatment of the anemia is to decrease the mass of myeloid tissue in the marrow by radiation or

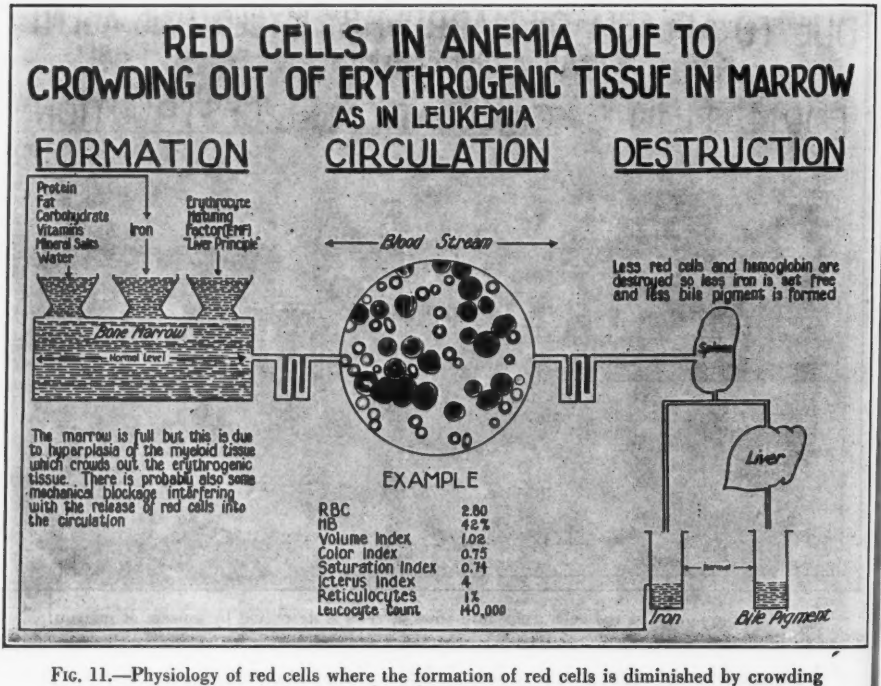


FIG. 11.—Physiology of red cells where the formation of red cells is diminished by crowding out of erythrogenic tissue.

medication to make room for the erythrogenic tissue. The red cell count often reveals more in leucemia than the number of white cells as it gauges the state of hyperplasia of the marrow which is more important than the white cell count.

Instead of a quantitative decrease in erythrogenic tissue, the total amount may be unchanged but the function be quantitatively depressed.

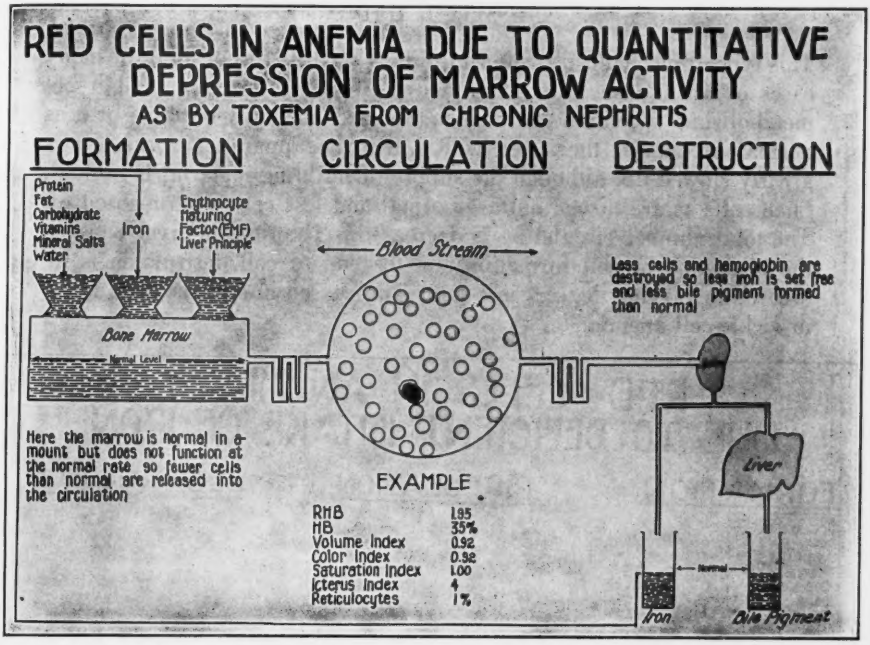


FIG. 12.—Physiology of red cells when the function of marrow is slowed up.

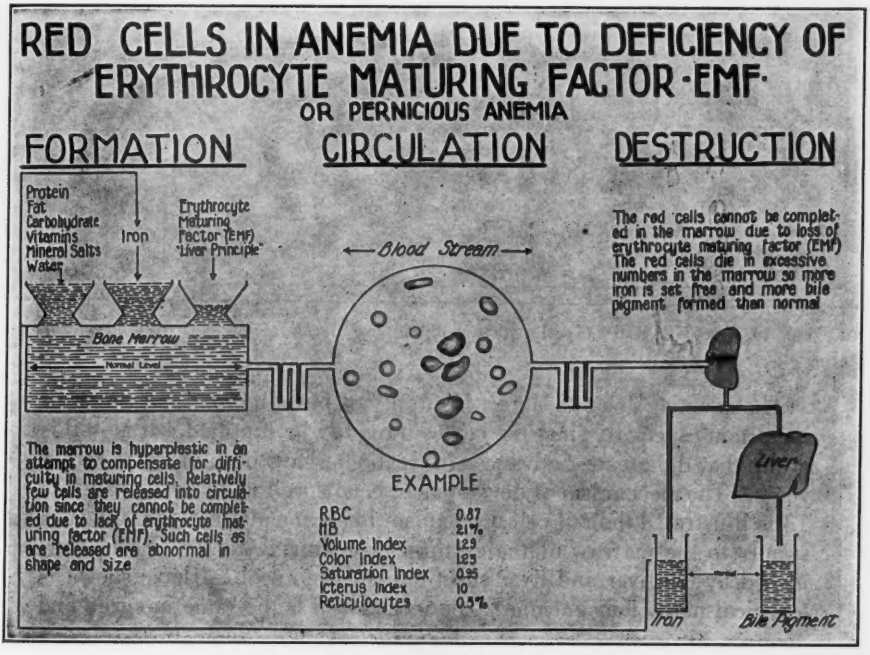

RED CELLS IN ANEMIA DUE TO DEFICIENCY OF ERYTHROCYTE MATURING FACTOR-EMF-
OR PERNICIOUS ANEMIA
FORMATION
CIRCULATION
DESTRUCTION
Protein
Fat
Carbohydrate
Vitamins
Mineral Salts
Water
Iron
Erythrocyte Maturing Factor (EMF) 'Liver Principle'
Bone Marrow
Normal Level
Blood Stream
The marrow is hyperplastic in an attempt to compensate for difficulty in maturing cells. Relatively few cells are released into circulation since they cannot be completed due to lack of erythrocyte maturing factor (EMF). Such cells as are released are abnormal in shape and size
The red cells cannot be completed in the marrow due to loss of erythrocyte maturing factor (EMF) The red cells die in excessive numbers in the marrow so more iron is set free and more bile pigment formed than normal
EXAMPLE
RBC 0.87
HB 21%
Volume Index 1.29
Color Index 1.23
Saturation Index 0.95
Icterus Index 10
Reticulocytes 0.3%
Liver
Normal
Iron
Bile Pigment

FIG. 13.—Physiology of red cells when building materials are deficient (pernicious anemia).

This type of mechanism is shown in Fig. 12. It is responsible for many cases of anemia such as malignancy, infections, toxemia, and hypometabolism. We can best visualize this mechanism by thinking of it as normal except for the speed with which the apparatus works. It is greatly slowed up, although the supply of building material is normal. Such cells as are turned out are normal and less cells are disposed of. The total number circulating is decreased. The time interval between the beginning of cell formation and the end of cell destruction is increased to varying degrees just as it is decreased in spherocytic anemia or sickle-cell anemia.

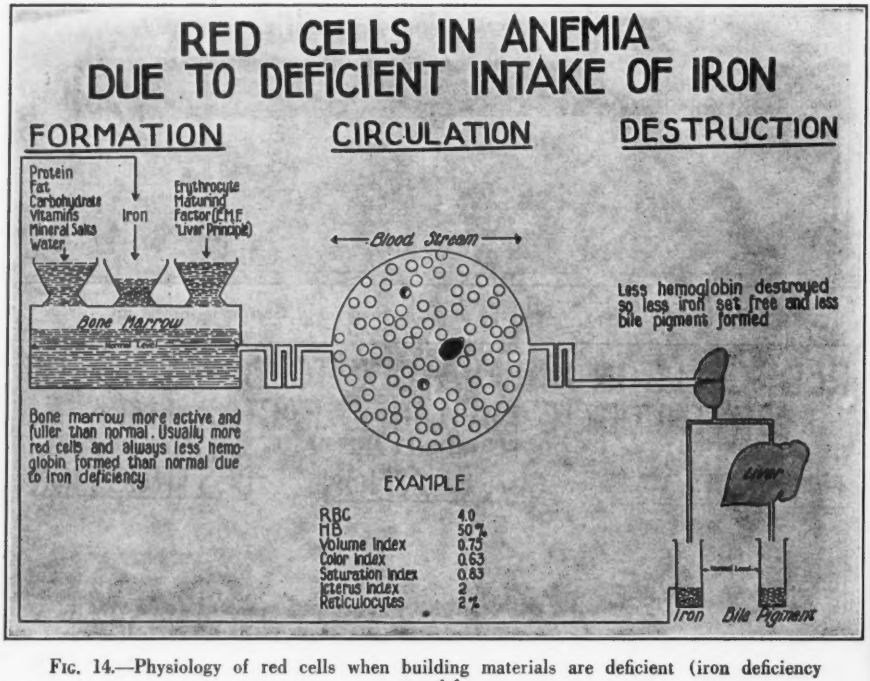


FIG. 14.—Physiology of red cells when building materials are deficient (iron deficiency anemia).

The anemias due to a defect in supply of building material are most important especially since the lack can readily be supplied. It is in this group that the greatest advances in treatment have been made in recent years. The mechanism of development is now well understood. In Fig. 13 is illustrated the red cell mechanism in an anemia due to a defect in supply to the marrow of the erythrocyte maturing factor (EMF) furnished by the liver and liver substitutes. The anemia I have shown is a typical pernicious anemia. The mechanism is the same in sprue and

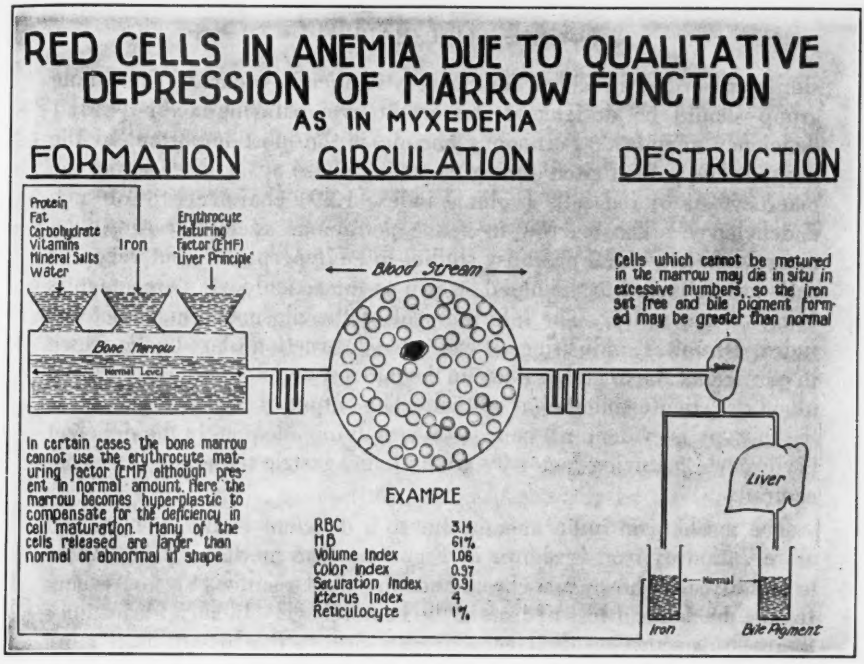

RED CELLS IN ANEMIA DUE TO QUALITATIVE DEPRESSION OF MARROW FUNCTION
AS IN MYXEDEMA
FORMATION
CIRCULATION
DESTRUCTION
Protein
Fat
Carbohydrate
Vitamins
Mineral Salts
Water
Iron
Erythrocyte Maturing Factor (EMF) "Liver Principle"
Bone Marrow
Normal Level
Blood Stream
Cells which cannot be matured in the marrow may die in situ in excessive numbers, so the iron set free and bile pigment formed may be greater than normal
In certain cases the bone marrow cannot use the erythrocyte maturing factor (EMF) although present in normal amount. Here the marrow becomes hyperplastic to compensate for the deficiency in cell maturation. Many of the cells released are larger than normal or abnormal in shape
EXAMPLE
RBC 3.14
HB 61%
Volume Index 1.06
Color Index 0.97
Saturation Index 0.91
Icterus Index 4
Reticulocyte 1%
Liver
Normal
Iron
Bile Pigment

FIG. 15.—Physiology of red cells when the marrow is unable to utilize the erythrocyte maturing factor (EMF) normally.

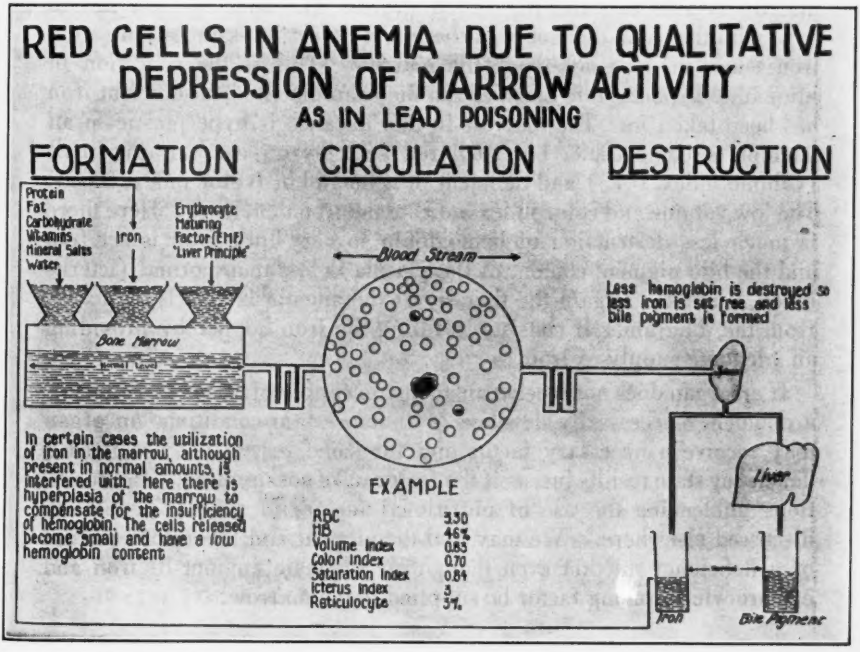

RED CELLS IN ANEMIA DUE TO QUALITATIVE DEPRESSION OF MARROW ACTIVITY
AS IN LEAD POISONING
FORMATION
CIRCULATION
DESTRUCTION
Protein
Fat
Carbohydrate
Vitamins
Mineral Salts
Water
Iron
Erythrocyte Maturing Factor (EMF) "Liver Principle"
Bone Marrow
Normal Level
Blood Stream
Less hemoglobin is destroyed so less iron is set free and less bile pigment is formed
In certain cases the utilization of iron in the marrow, although present in normal amounts, is interfered with. Here there is hyperplasia of the marrow to compensate for the insufficiency of hemoglobin. The cells released become small and have a low hemoglobin content
EXAMPLE
RBC 3.30
HB 46%
Volume Index 0.85
Color Index 0.70
Saturation Index 0.84
Icterus Index 3
Reticulocyte 3%
Liver
Iron
Bile Pigment

FIG. 16.—Physiology of red cells when the marrow is unable to utilize iron normally.

similar disorders in which the macrocytic anemia occurs. This whole group should be designated the erythrocyte-maturing-factor (EMF) deficiency anemias. Pernicious anemia is the most important of the group. The patient cited during the active phase of the disease had the macrocytosis of red cells (volume index, 1.29) characteristic of such a deficiency. The marrow in active pernicious anemia is shown by marrow puncture and necropsy studies to be hyperplastic, but very few cells are delivered to the blood stream so the reticulocyte percentage is low (0.5 per cent). The bile pigment of the plasma is high (icterus index, 10 units), indicating an excessive destruction of red cells which in pernicious anemia takes place in the marrow and not in the circulating blood or reticulo-endothelial system. The output of iron is high. Here the therapy is evident. It consists in supplying adequately the deficient erythrocyte maturing factor by giving liver, gastric tissue, or liver concentrates.

The mechanism in an anemia due to a deficient intake or impaired assimilation of iron is shown in Fig. 14. The mechanism is similar to that already shown in a chronic hemorrhagic anemia (Fig. 5) except for the mechanical loss of iron in the hemorrhage. In such an instance there is also an iron deficiency anemia due to the loss of iron more rapidly than it is normally supplied by food. If sufficient iron is given, the hemorrhage may continue, but the anemia is relieved so long as the marrow is able to stand the added strain. The bone marrow has to cope with the same deficiency if there is a defect in assimilation so the iron taken in does not reach the marrow. This is the condition in idiopathic hypochromic anemia. In the example cited, insufficient iron has been taken in. The marrow in this instance is hyperplastic in an attempt to compensate, but such red cells as do get out are small (volume index, 0.75) and deficient in hemoglobin (color index, 0.67). The low volume and color index indicate the iron deficiency. Here there is much less destruction of hemoglobin so very little iron is set free and the bile pigment content of the plasma is less than normal (icterus index, 2 units). Again the therapy of the anemia is clearly indicated from the diagram. It consists in filling the iron hopper by providing an adequate supply of iron.

If an organ does not receive an adequate supply of a necessary factor, a deficiency necessarily develops. Under certain conditions an organ may receive a necessary factor and for some reason not use it so a deficiency state results just as if the factor were not supplied. The conditions influencing the use of nutritional factors in general have been discussed elsewhere.[7] We may find the clinical and laboratory picture of a deficiency anemia even though an adequate amount of iron and erythrocyte maturing factor be supplied to the marrow.

It is well known that myxedema may show the typical blood picture of pernicious anemia. Such a state is illustrated in Fig. 15. This patient had an anemia with a mild macrocytosis in myxedema. The defect is in the normal completion of the red cells just as it is in idiopathic pernicious anemia. In such a case, the addition of thyroid extract alone should relieve the anemia since the marrow can then use the erythrocyte maturing factor (EMF) already supplied in adequate amounts.

It is quite common to encounter an iron deficiency anemia which will not respond to adequate dosage of iron. There seem to be many more extraneous factors influencing the use of iron by the marrow than of the erythrocyte maturing factor. The example cited in Fig. 16 is the case of a patient with lead poisoning. The giving of iron does not influence the anemia, although the laboratory findings of low volume and color index are characteristic of an iron deficiency anemia. The lead seems to prevent the normal utilization of the iron by the marrow, so treatment must first consist of removing the influencing factor before iron is given. The findings here are exactly like those shown in chronic hemorrhagic anemia (Fig. 6), and an anemia due to a deficient intake of iron (Fig. 14). The laboratory findings indicate the fundamental defect so far as the marrow is concerned but do not show whether the marrow defect is due to excessive loss, deficient intake, or impaired utilization of iron.

Summary

In every case of anemia, the rate of red cell formation and delivery from the marrow, the rate of destruction, and the balance between these two factors must be determined.

Measures are available for gauging accurately the state of the marrow and all important factors in red cell activity.

The anemia must be studied and classified from both the clinical and laboratory standpoints.

Red cell formation, circulation, and destruction in all the common anemias are illustrated by diagrams.

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ILLUSTRATIVE CASES OF CONTACT DERMATITIS

E. W. NETHERTON, M. D.

Contact dermatitis is a term used to designate the inflammatory reaction which occurs in the skin of individuals following contact with substances to which they are sensitive. The types of agents which may produce a contact dermatitis vary greatly, are innumerable, and are distinguished from common irritants in that most individuals are not affected by single or repeated contacts with them. The medical literature is replete with articles which list the various agents capable of producing a dermatitis and each year new items are added. With the development of industry, the hazard from contact with chemicals has greatly increased the incidence of occupational dermatoses. Likewise, the almost universal use of cosmetics is responsible for a large number of cases of contact dermatitis involving the face, neck, and upper portions of the trunk. Weber[1] has recently published a complete list of the irritants known to produce a dermatitis in susceptible individuals and his article is well worth the attention of anyone interested in this subject.

Since contact dermatitis is one of the most common of dermatological conditions, it would seem that a brief discussion of a few cases would be of interest.

Case 1: A married woman, 32 years of age, came to the Clinic because of an eruption in the axillae; this had been present for the preceding two months. Roentgen therapy and various topical applications had produced temporary relief, but she had continued to have recurrences and exacerbations of the eruption. The inflamed skin was so tender that she was unable to dress comfortably. Itching was also a troublesome symptom.

The past history, physical examination, and laboratory findings were unimportant. The eruption was symmetrical and limited to the axillae and adjacent skin (Fig. 1). Each axilla was surrounded by a fairly well demarcated, subacute, erythematous, vesicular, crusted dermatitis. The skin in the axillae was erythematous and crusted only in a few small areas. Each axillary region was involved by a large inflammatory plaque. The more inflammatory, vesicular, crusted periphery involved the anterior and posterior axillary folds, the under surfaces of the arms, and the subaxillary skin. The vesicles at the periphery of the plaques were large, superficial, and ruptured easily. The crusts which formed at the site of the ruptured vesicles were fairly adherent and were surrounded by erythematous, bullous areolae; consequently the surface epithelium could easily be removed well beyond the margins of the crust. Many of the individual lesions were impetiginous in type. The feet and groins were free from signs suggestive of an epidermophyton infection and fungi were not observed in material removed from the periphery of the dermatitis.

The patient had been troubled with hyperhidrosis of the axillae for several years. She denied using deodorants and astringents but had worn dress shields to protect her clothing. Patch tests were done with material from a shield

which she had worn to the Clinic. The results of the test were negative. Since this shield was old and had been washed several times, it was thought advisable to apply tests with material from a new shield.

The type of shield which she wore was, according to the manufacturer, made from pure Ceylon rubber compounded with insoluble pigments. The shield

FIGURE 1: Photograph showing eruption limited to axilla and adjacent skin (Case 1).

gum was surfaced with pure cotton flock. Both the rubber sheet and the cloth covering of the new shield were used for patch tests. Each material produced a marked eczematoid dermatitis (Fig. 2). Apparently the noxious substances could be removed by washing the shield with soap and water.

The eruption responded well following the application of a bland boric and zinc oxide ointment. The patient was advised to either change to another

type of dress shield or to wash the new shields before wearing them. This patient lived out of the city and we were unable to make more detailed investigations. She promised to report if a recurrence developed, and since

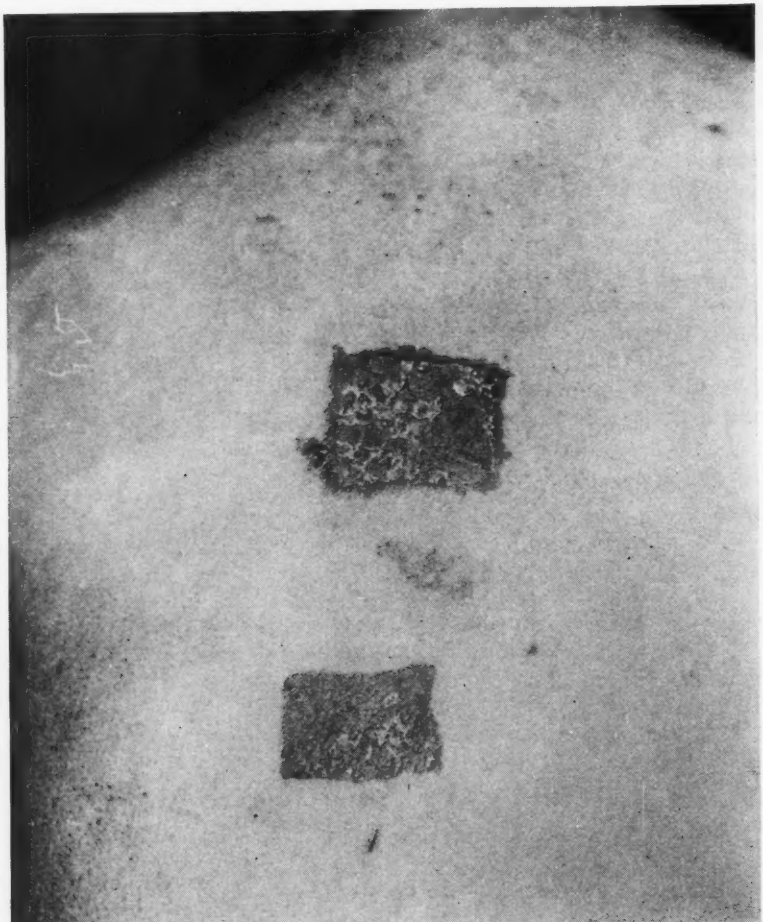

FIGURE 2: Marked eczematoid dermatitis produced by patch tests using rubber sheet and cloth covering from dress shield. Upper—rubber from shield. Lower—cloth from shield. Photograph taken five days after test patch was removed.

she has not been seen for more than five months, we assume that she has remained well.

Comment: This case should probably be classified as one of rubber sensitization. The well-defined inflammatory margins and the more or less clearing of the central portions of the areas of dermatitis readily

suggest the possibility of a ringworm infection, particularly since the axillae were involved. However, the impetiginous crusting and the large vesicles are not ordinarily seen in uncomplicated cases of ringworm infection of the axilla. The absence of lesions on the feet or in the groins and finally the failure to demonstrate fungi in the material from the lesions are points against the diagnosis of a fungous infection.

The more inflammatory reaction at the margins of the lesion was probably due to the concentration of the irritant at the periphery of the shield. The irritant which can be removed from the shield with soap and water is also soluble in perspiration and is carried in solution to the circumference of the shield by the force of gravitation.

The absence of impetiginous lesions beyond the periphery of the areas of dermatitis or elsewhere on the body is against the diagnosis of an impetiginous dermatitis.

Case 2: A married woman, 66 years of age, came to the Clinic on June 26, 1937. Except for discomfort due to an old fracture of the coccyx, her health had previously been good. She usually perspired freely during the warm summer months. On May 26, 1937, a red, itchy spot developed in the left axilla. This lesion continued to enlarge and in a few days a similar lesion appeared in the right axilla. The eruption continued to spread and soon involved the neck, chest, back, and posterior surface of the thighs. She had obtained some relief following the use of a lotion and powder which had been advised by her physician; however, with the advent of warm weather the eruption and itching had become much worse. Her symptoms were aggravated when she perspired.

There was a subacute, eczematoid dermatitis involving the axillae, neck, chest, back, the under surface of each arm, and the posterior surface of the thighs. The portions of the trunk which were covered by her girdle and brassiere were not involved. The eruption encircled the chest at the level of the axillae. The lower portion of the eruption was fairly well demarcated at the upper margin of the brassiere. In addition, there was a small band of dermatitis on the areas covered by the shoulder straps of the slip. The inflammatory reaction was more intense in the axillae, on the posterior surface of the thighs, and on the back, this being due to the hyperhidrosis and the close contact of the skin with the clothing in these areas (Figs. 3, 4, 5, and 6). In these areas, there was vesiculation, weeping, and crusting.

It seemed apparent that the dermatitis in this case was probably caused by the dye in the patient's clothing. A blue slip which she was wearing was the only new garment she had purchased for several months. She was also wearing a blue dress which she had had for several months. The dye of the slip faded while that of the dress remained fixed. A diagnosis of dermatitis venenata due to dye in the slip was made.

The following patch tests were applied:

1. Axillary portion of slip
2. Hem of slip
3. Axillary portion of dress
4. Hem of dress

The material from the dress gave a negative reaction while that from the slip produced edema, erythema, and vesiculation.

The eruption subsided rapidly after the slip was discarded. A bland ointment consisting of one per cent phenol and equal parts of boric acid and zinc oxide was advised.

FIGURE 3: Eczematoid dermatitis involving the axilla (Case 2).

Comment: The characteristics of the eruption in this case were so striking that there could be little doubt that the dye of a garment was the causative irritant. Hyperhidrosis is considered to be a predisposing cause of this type of dermatitis and this is well illustrated by this case.

Case 3: A married woman, 20 years of age, came to the Clinic on May 25, 1937, complaining of an eruption about the eyes and in the axillae. In September, 1936, she had a dermatitis on the eyelids which was attributed to the use of cosmetics. After this cleared up, she remained well until March, 1937, when she had a recurrence of the eruption about the eyes. This disappeared in about three weeks. She then remained free from any eruption until one week before coming to the Clinic. At this time a dermatitis had developed in the axillae, on the chest, and there was a recurrence of the eruption on the face. The only cosmetic which she had used during the preceding three weeks was a lipstick; however, she had been applying "Quest" deodorant powder to the axillae. She had purchased two new navy blue dresses.

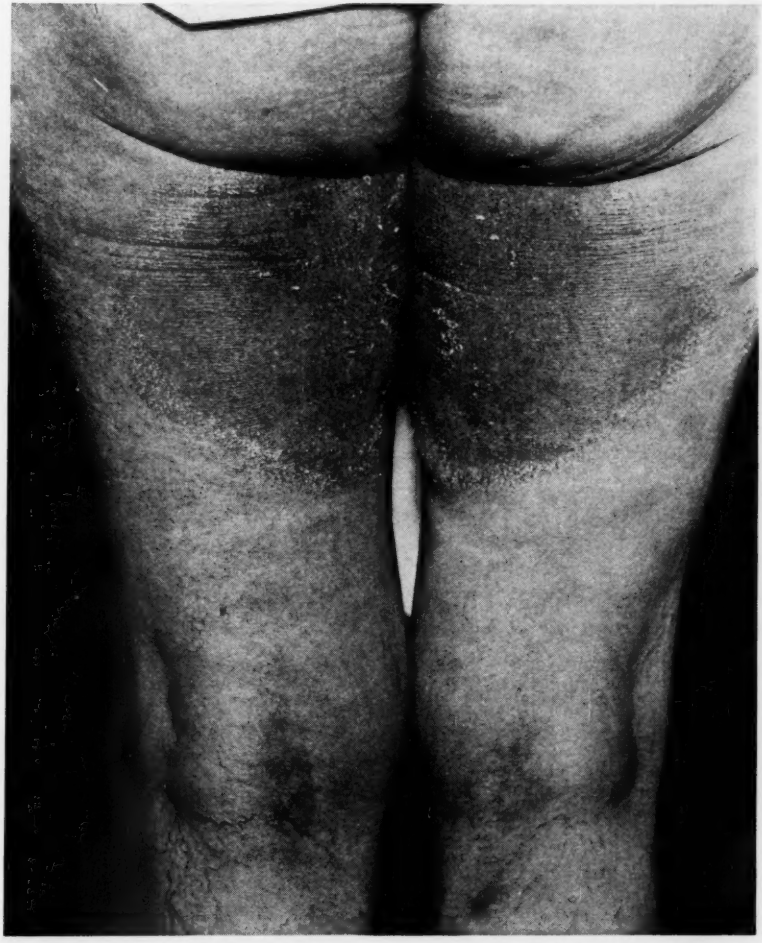

FIGURE 4: Eczematoid dermatitis involving posterior surface of the thighs (Case 2).

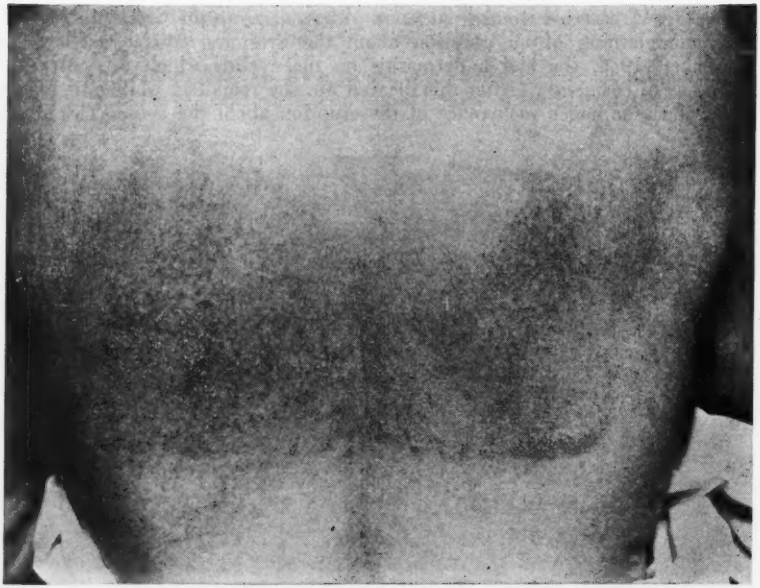

FIGURE 5: Eczematoid dermatitis involving the back (Case 2).

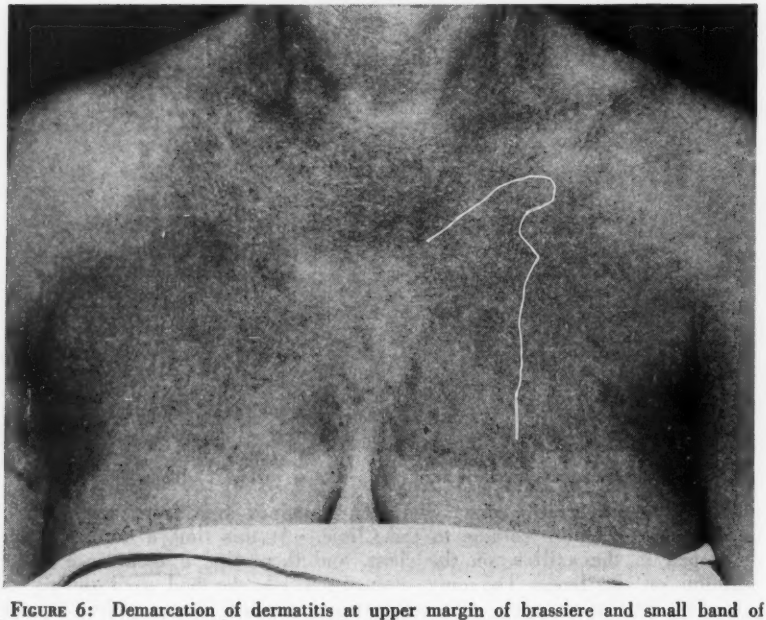

FIGURE 6: Demarcation of dermatitis at upper margin of brassiere and small band of dermatitis in area covered by straps of slip (Case 2).

There was a poorly demarcated, subacute, erythematous, scaly dermatitis on the face and about the eyes. The eyelids were edematous. The dermatitis on the chest and in the axillae was more acute and erythematous.

Various substances with which the patient came in contact were used for patch tests. At first the following results were obtained:

Rotogravure paper* ++++	Patient's rouge +
Material from black dress +	Scouring powder —
Material from blue dress —	"Quest" deodorant —
Patient's face powder —	Dust rag —
Patient's lipstick +	

The reaction to rotogravure paper was marked (Fig. 7). However, the results of these tests did not satisfactorily explain the presence of the dermatitis on the trunk. The patient was advised to stop wearing the black dress, to avoid rotogravure paper, and to change to a nonallergic brand of cosmetics. Following this, the dermatitis practically disappeared, but five weeks later a recurrence developed on the face, the upper portion of the trunk, and on the hands. This dermatitis was more severe than that experienced in the past. At this time, many small vesicles developed and the site of the previous patch test with rotogravure paper became eczematoid. The afternoon before this recurrence she had worn, for the second time, a new navy blue crepe dress. Otherwise her contacts had not changed. She was asked to bring in all colored dresses for patch testing. Patch tests with two navy blue dresses gave a strongly positive reaction. A black dress produced a slight erythematous dermatitis and a second test with rotogravure paper again produced a severe eczematoid reaction. The dermatitis completely disappeared following the applications of moist packs of an aqueous solution of aluminum acetate (1:20 solution) and calomine liniment. The patient has not returned for further observation.

Comment: This patient had a multiple sensitization and it is probable that other irritants not yet determined may have been factors in the causation of the recurrences of dermatitis. In both this case and the previous one, the dermatitis was due to a blue dye. These cases are similar to the ones reported by Bonnevie and Genner[3] who collected 15 cases of eczema due to dyed clothing. In nine of their cases, a blue dye was shown to be the cause of the dermatitis. They emphasized that hyperhidrosis is a predisposing factor in this type of eczema. These authors observed that eczema, due to dyed garments, frequently became chronic and remained for several months after the noxious clothing had been discarded.

Case 4: A single woman, 25 years of age, came to the Clinic on July 15, 1937. For three months she had had a dry, thickened, scaly plaque limited to the left palm. She had never had a fungous infection on her feet. Three days prior to our first observations, stomatitis and an eruption about the mouth and on the lateral surfaces of the fingers of the right hand developed.

There was a poorly demarcated, brownish red, scaly and slightly thickened plaque in the central portion of the left palm. The scales were dry and adherent. The plaque was not indurated and there were no fissures along

*Oliver[2] has reported dermatitis to rotogravure ink.

the normal markings of the palm. On the lateral surfaces of the fingers of the right hand and on the webs between the fingers, there was a more acute erythematous, vesicular dermatitis. The vesicles were small and superficial. The dermatitis about the corners of the mouth was similar to that

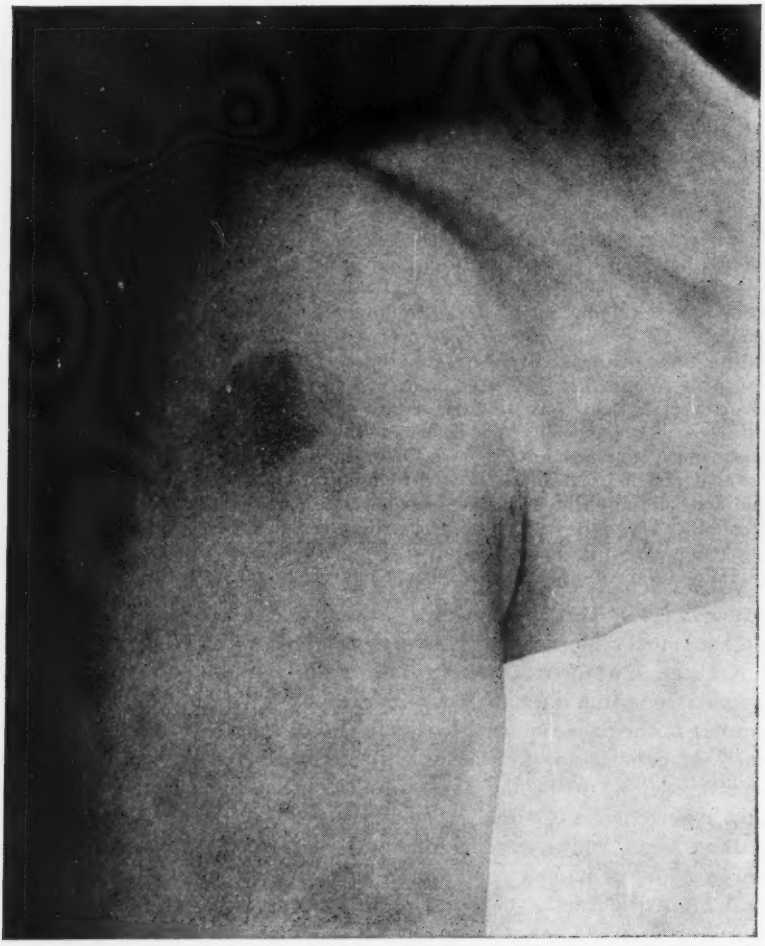

FIGURE 7: Patch test showing marked reaction to rotogravure paper (Case 3).

on the right hand. The gums were acutely inflamed. The presence of an acute dermatitis on the right hand and about the mouth suggested the possibility of a dermatitis venenata while, in the differential diagnosis of the chronic dermatitis of the left palm, the possibility of ringworm infection or a contact dermatitis had to be considered.

The history revealed that three months prior to the appearance of the eruption on the left palm, the patient had changed her dentifrice and during

this time she had used a nationally advertised tooth powder (Pepsodent). She had used this dentifrice three months before the lesion appeared in the left palm and about six months before the stomatitis and acute dermatitis about the mouth and on the right hand developed. In using this dentifrice, she placed the powder in the left hand and brushed it up with a wet tooth brush which she held in her right hand. While she was cleansing her teeth, some of the powder and water usually trickled onto the fingers of the right hand.

It was apparent that all the lesions in this case could be caused by this dentifrice. Powder from the container which the patient had used for some time was used for patch testing. The powder produced an erythematous, vesicular dermatitis when it was applied to the flexor surface of the forearm (Fig. 8).

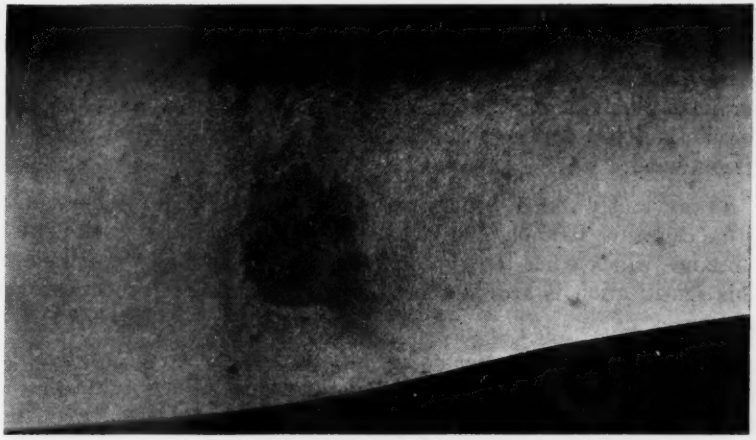

FIGURE 8: Patch test showing marked reaction to tooth powder (Case 4).

The manufacturer of this dentifrice was kind enough to send us samples of the soluble and insoluble ingredients. The patient was tested with each ingredient and all of them failed to produce a dermatitis. We had no explanation for this discrepancy. It seemed that either the manufacturer failed to send samples of all ingredients or that the ingredients in solution were not in the strength used in the manufactured product. It was suggested that a product of a chemical reaction between the ingredients might be the causative irritant. Therefore a paste made by mixing all of the ingredients which were obtained from the manufacturer was applied as a patch test. At the end of 48 hours when the patch was removed, there was a positive but much less intense reaction.

Following this investigation, a new can of this dentifrice was purchased and a second patch test was applied. The test was strongly positive.

The stomatitis and all the cutaneous lesions in this case disappeared when the use of the tooth powder was discontinued.

Comment: It was not difficult to make the diagnosis in this case when the patient first came under observation; however, it is very doubtful

whether the correct diagnosis would have been made during the time when the eruption was limited to the left palm.

If the cause of the dermatitis can be determined and eliminated, the results are excellent and the patient is, of course, very grateful. However, this frequently is not obtained as easily as one would expect. In some cases the causative agents may be determined in a comparatively short period while at other times a prolonged search is necessary before all the etiologic factors can be elicited. In some cases the cutaneous reaction has been so severe as to terminate in a generalized exfoliative dermatitis which may not disappear for several weeks after the primary irritant has been removed. Patients suffering from a contact dermatitis of an occupational origin are frequently confronted with the additional problem of changing their occupations. Unfortunately, this can seldom be done easily or without material loss. It is well to remember that the dermatitis due to certain chemicals, particularly dyes, is apt to become chronic and last for weeks after contact with the chemical has been discontinued.

As previously stated, a person with a contact dermatitis is sensitive to the causative irritant. Why some individuals become sensitive to a substance which other individuals tolerate with impunity is unknown. This sensitization is acquired usually after repeated contact with the substance.

The sensitizing properties of agents or allergens vary considerably. It is conceivable that some individuals may develop a sensitization to any chemical. The number of exposures, the interval between the contacts, and the appearance of the dermatitis also vary with different individuals and with different allergens. These important facts must be kept in mind if one is to avoid being influenced by the statements and arguments of the patient. Frequently, patients will insist that a certain substance could not be the cause of the dermatitis because their friends use or come in contact with the same substance without suffering any ill effects, or that they have used a certain preparation, such as a cosmetic for instance, for several weeks or months without trouble.

The successful management of the type of patient under consideration necessitates a careful evaluation of the clinical characteristics of the eruption and an accurate, detailed history. The history is very important and unless the physician can obtain the cooperation of the patient, the solution of some cases becomes extremely difficult.

A dermatitis due to an external irritant is usually limited to or is more marked on the face, neck, hands, and arms or the exposed portions of the body. In instances where the covered portions of the body are involved, the distribution and arrangement of the eruption is such as to

suggest the possibility of some external irritant. For example, limitation of the eruption to the skin just beneath the trouser or shirt pocket suggests the possibility of a match dermatitis; limitation of a plaque to the skin of the thigh which comes in contact with the metal supporter of a girdle suggests the possibility of nickel as the irritant. The presence of a symmetrical eruption limited to the feet and legs which are covered by the socks points to the dye of the socks as the causative agent. The dermatitis produced by the varnish on the toilet seat is another familiar type of contact dermatitis which may occur on portions of the body which are usually covered with clothing. Many other examples could be cited but these are sufficient to emphasize the importance of carefully noticing the distribution of an eruption. This is particularly important in patients with contact dermatitis.

The clinical manifestations of dermatitis venenata vary considerably and are not characteristic for any particular type of irritant. The inflammatory reaction may be mild, severe, acute, subacute, or chronic. The eruption is eczematoid in type, consisting of erythema and edema, and accompanied by vesiculation, weeping, scaling, and crusting. In the more chronic type of dermatitis, the papular lesions predominate and the skin may become lichenified. Oftentimes the lesions have a predilection for the follicles of the skin. This is because the irritant can more easily penetrate and become lodged within the cutaneous follicles. The eruption as a rule is poorly demarcated and the intensity of the inflammatory reaction at the periphery of the dermatitis usually fades gradually into the adjacent normal skin. Itching is generally a prominent symptom.

The physician should in most cases be able to determine whether a diagnosis of contact dermatitis is tenable if he has carefully and systematically observed the distribution and characteristics of the eruption. The next and most important procedure is to obtain a careful history. This cannot be accomplished in a few minutes. The physician must have patience and a cooperative patient. The age, sex, social status, and occupation serve as initial leads for the history. The possibility of contacts with substances which are commonplace, with additional information pertaining to contacts relative to the patient's environment and habits, will usually give clues which lead to the ultimate discovery of the causative irritant. Information obtained from the history will suggest certain irritants which may be the cause of the dermatitis. The next step is to test the patient for susceptibility to these irritants. This is done by using the patch test method devised by Jadassohn. The irritant to be tested is applied to a small piece of white linen and applied to the normal skin. This is covered with a piece of cellophane and the patch is held in place with broad pieces of

adhesive tape. Preparations such as face powder, cold cream, rouge, etc., are applied unchanged. When testing a suspected chemical such as soap, which under ordinary circumstances does not remain on the patient's skin for any length of time, it is best to start the investigations with weak dilutions of the substance. Control tests should be done on normal individuals when testing for substances which have not been shown to be common irritants. The patch test is held in contact with the normal skin for 24 or preferably 48 hours. At the end of this period, the patches are removed and the degree of inflammatory reaction observed. An eczematoid reaction with erythema, edema, and vesiculation is classified as a four plus reaction. Further details of the technic of the patch test method such as substitutes for adhesive tape in persons sensitive to the adhesive cannot be discussed here. Suffice it to say that the patch test is a comparatively simple procedure which can be used safely by any physician.

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ENDOMETRIOSIS

A Clinical Study of 37 Cases

GEORGE CRILE, JR., M. D.

Endometriosis is defined as "the presence of endometrial tissue in ectopic locations." Endometrial tissue may be implanted on the ovaries, on the pelvic peritoneum, in the umbilicus, in the rectovaginal septum, or in laparotomy scars. It functions as endometrium, undergoing the cyclic changes characteristic of menstruation. It is, therefore, capable of forming cysts of retained blood (chocolate cysts) and of producing pain at the time of menstruation.

The etiology of endometriosis is still in dispute. The theory of J. A. Sampson[1] is that cast-off endometrium from the uterine cavity regurgitates through the tubes at the time of the menstruation and results in an implantation of endometrial cells in the peritoneum. The theory of German authors, supported by E. Novak[2], postulates the metaplasia of peritoneal cells to endometrial cells. Each theory seems to explain certain types of endometriosis but neither offers a completely satisfactory explanation for all cases.

SYMPTOMS

Although extensive endometriosis may be present without causing symptoms, this condition usually produces considerable pain. In 10 of the 37 cases in this series, endometriosis was an incidental and symptomless finding in the course of pelvic operations performed for other causes.

In the remaining 27 cases, in all of which the diagnosis was confirmed at operation or by microscopic examination of removed tissue, pain was an outstanding feature of the history. In the great majority of the cases, the pain was more severe at the time of menstruation.

TABLE I

SYMPTOMS IN 27 CASES OF ENDOMETRIOSIS

Symptom	*Number of Patients*
Dysmenorrhea	17
Pain in lower abdomen	16
Pain in back	5
Pain in scar of previous operation	2
Pain on defecation	1

Exacerbations of pain tend to occur during the week before the onset of each menstrual period and often (three cases in this series) the patients state that the dysmenorrhea is worse before the onset of the menses than at any other time.

Symptoms of endometriosis necessarily occur during the active part of a woman's menstrual life and symptoms rarely persist after cessation of the menses. The oldest patient in this series was 52 and the youngest 26, the average age of the 37 patients being 37½ years. Twenty-six of the patients were married and 50 per cent of these had been married from three to 19 years without conception. Twenty-seven per cent of the patients had had from one to four pregnancies (an average of two) but as a rule a prolonged period of sterility had followed one or two pregnancies early in married life.

Menorrhagia was a symptom of 35 per cent of the patients. In the majority of cases the bleeding could be explained by the presence of uterine fibroids. It is interesting, nevertheless, to note that more than 24 per cent of the 37 patients in this series had fibroids of the uterus, endometriosis, and menorrhagia. This association has been noted in other series of cases and cannot fail to suggest that there may be an underlying endocrine factor which could well be responsible for all three conditions.

Operative Findings

Chocolate cysts of the ovary were found in 26 of the 37 cases in this series. These cysts varied in size from 1 cm. to 15 cm. in diameter

Table II

OPERATIVE FINDINGS—37 CASES OF ENDOMETRIOSIS

Location	*Number of Cases*	*Percentage of total number of cases*
Chocolate cysts of ovary	26	70
Implants on posterior surface of uterus and in region of uterosacral ligaments	13	35
Implants or chocolate cyst in abdominal wall at site of previous laparotomy scar	4	11
Implants on appendix	2	5
Implants on broad ligament	2	5
Implants on peritoneum over bladder	2	5
Implants on tubes	1	3

and were bilateral in many cases. The posterior surface of the uterus and the region of the uterosacral ligaments were the favorite sites of endometriosis of the pelvic peritoneum.

Uterine fibroids were present in 46 per cent of the cases, and a fixed retroversion of the uterus was observed in 14 per cent. Chronic salpingo-oophoritis was found in one case and a primary carcinoma of the fallopian tube which was believed to arise from ectopic endometrial tissue was present in one instance.

Diagnosis

As a result of the frequency with which fibroids and retroversion of the uterus are associated with endometriosis, it is not surprising to find that in the majority of cases the diagnosis of endometriosis was not made, attention being focused on the more obvious disorders that were easily palpable on pelvic examination. It should be remembered that acquired dysmenorrhea or persistent pelvic pain is not usually caused by uncomplicated retropositions or by uterine fibroids of medium size. If it is discovered that the dysmenorrhea starts before the onset of the menstrual flow and consists of persistent localized pain rather than of uterine cramps, and if in addition to this the patient gives a history of sterility, either relative or absolute, then the diagnosis of endometriosis should be made. Unfortunately, however, the symptoms and the physical findings are so variable that it is not possible in all cases to make the diagnosis before operation.

Operation

When, in the course of an operation on a young woman, the surgeon finds extensive endometriosis of the pelvic viscera, he is called upon to make a most difficult decision. The problem is usually rendered more complex because the diagnosis of endometriosis has often been unsuspected before operation and the surgeon has not discussed with the patient the possibility of this finding. The operator must decide whether it is best to perform a conservative operation, preserving the menstrual function and the possibility of pregnancy, or whether bilateral oophorectomy is justified.

If the surgeon decides upon the conservative course, he will, in all probability, fail to relieve the patient's symptoms in approximately 17 per cent of the cases, and later will be forced to recommend the additional expense and discomfort of either a secondary operation or of sterilization with x-ray. On the other hand, if he performs a radical operation, the patient loses all hope of subsequent pregnancy, the menstrual function is abolished, and the menopause is artificially induced.

End Results

Ten of the 37 cases in this series were excluded because the endometriosis was an incidental finding unrelated to the patient's symptoms and five were excluded for lack of follow-up data. There remain then 22 cases in which the patients were followed for an average period of four years and in which the endometriosis was responsible for the patients' symptoms. Eighty-six per cent of these patients obtained complete relief from their symptoms following operation. One patient (five per cent) obtained partial relief, and the remaining 9 per cent obtained no relief.

In 10 cases both ovaries and in the majority of cases the uterus as well were removed. All these patients remained entirely symptom-free. This type of therapy was generally reserved for the older patients, the average age of the patients in this group being 40 years.

The three failures to obtain complete relief after operation occurred in the group of 12 cases in which ovarian tissue was conserved. In one of these cases the persistent discomfort was sufficiently severe to necessitate interruption of the menses by x-ray therapy to the ovaries. The average age of the patients in this group was 34, six years younger than the group in which all ovarian tissue was removed.

Table III

END RESULTS IN 22 OPERATIONS FOR ENDOMETRIOSIS

Treatment	*Number of cases*	*Average age*	*Average length of follow-up*	*Complete relief*	*Partial relief*	*No relief*
Radical (bilateral oophorectomy)	10	40 years	36 months	100%	0	0
Conservative (one or both ovaries left)	12	34 years	58 months	75%	8%	17%

It is interesting to note that none of the 10 patients in whom bilateral oophorectomy was performed complained of any severe symptoms referable to the menopause. Although alteration in ovarian activity may be a factor, the most likely explanation of this observation is that the patient with endometriosis has usually experienced such severe pain for so many years that the relief afforded by the artificial menopause overshadows the menopausal symptoms and makes the patient grateful and happy to be free from pain. In only one case in the entire group—the patient who had x-ray therapy for pain persisting after a conservative

operation—was it necessary to give sedatives or endocrine therapy to control menopausal symptoms.

Discussion

It is apparent from the data presented that the treatment of endometriosis may be unsatisfactory in a certain percentage of cases. Failure to relieve the patient's symptoms is not uncommon when reliance is placed upon an operation that preserves the menstrual function, whereas menopausal symptoms occasionally are troublesome when both ovaries are removed. In younger patients who wish to continue to menstruate and to have children, the abolition of menstruation and all possibility of pregnancy may cause considerable mental distress. A decision between the radical and the conservative course is difficult to make.

In patients beyond the age of forty, there is little excuse for preserving ovarian function at the risk of failure to relieve the patient's symptoms. The fact that menopausal symptoms in the patients of this group have been relatively mild would tend to make us more radical in our disposition of cases in which the symptoms have been severe and the endometriosis extensive. Yet we believe that, whenever it is possible, the patient should be consulted as to whether or not bilateral oophorectomy should be performed. If the patient clearly understands the possibility that a conservative operation may fail to relieve her symptoms and that subsequent x-ray therapy may be necessary and if, in spite of this, she desires to retain the menstrual function, then we believe that conservatism is indicated. But, when the patient is not desirous of becoming pregnant or continuing to menstruate, it is generally better judgment to remove the ovaries.

Since pregnancy so rarely occurs following conservative operations for endometriosis, since the patients do not as a rule complain of menopausal symptoms following radical operations, and since radical operations bring relief to practically 100 per cent of the patients so treated, the radical treatment would appear to give the most satisfactory results.

Summary

1. An analysis of 37 cases of endometriosis has been made.

2. The diagnosis should be suspected in all cases of acquired dysmenorrhea, especially when this is associated with a history of sterility.

3. The association with endometriosis of uterine fibroids and of retroversion of the uterus is very common, and acquired dysmenorrhea

or pelvic pain should not be attributed to these conditions without careful consideration of the possibility of a complicating endometriosis.

4. Conservative operations which left the uterus and sufficient ovarian tissue to maintain menstruation relieved the patients' symptoms in 75 per cent of the cases and failed to give any relief in 17 per cent.

5. Radical operations in which the uterus and both ovaries were removed gave relief of the patients' symptoms in 100 per cent of the cases and resulted in surprisingly few severe menopausal symptoms.

6. It is important to consider the possibility of endometriosis in any case in which a conservative operation for pelvic pain or acquired dysmenorrhea is planned.

7. If a conservative operation fails to afford relief of the patient's symptoms, a cure can generally be effected by abolishing the menses with x-ray therapy.

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1. Sampson, J. A.: Perforating hemorrhagic (chocolate) cysts of ovary, their importance and especially their relation to pelvic adenomas of endometrial type, Arch. Surg., 3:245, (September) 1921.

2. Novak, E.: Significance of uterine mucosa in fallopian tube with discussion of origin of aberrant endometrium, Am. J. Obstet. & Gynec., 12:484-526, (October) 1926.

TREATMENT OF UNDULANT FEVER BY ARTIFICIAL FEVER THERAPY

Report of Case

WALTER J. ZEITER, M. D.

Despite the fact that undulant fever is now recognized as a widespread and fairly prevalent disease, methods for its treatment are still somewhat uncertain. Brucellosis has in the past been treated chiefly by chemotherapy, vaccine, and serum therapy. The vaccines used have generally been of two types, specific Brucella vaccine or a fever producing vaccine, such as typhoid and paratyphoid A and B. From a review of many cases[1] reported during the past decade, it appears that the results obtained by the administration of a fever producing vaccine have been most gratifying. It was observed that the undulant fever disappeared more often in those patients in whom a febrile reaction had been obtained.

It has been demonstrated by many workers that fever induced by physical means is of value in any condition for which malarial, typhoid, or protein injection therapy is indicated. A recent report[2] indicated favorable results in four patients treated by artificial fever. In the following case, the patient responded very satisfactorily.

REPORT OF CASE

The patient, a married farmer, 54 years of age, was admitted to the Cleveland Clinic on April 30, 1937. His complaint was of pain in the scrotum with marked edema, pain in the left hip, right shoulder and the hands, weakness, and periods of diaphoresis.

Past history: About a year previous to examination—in April, 1936—the patient had pains in various joints. These were similar to those he was experiencing at the time of our examination and he stated that such pains had occurred nearly every spring for the preceding 10 years. He also had noticed a swelling of the right testicle, and weakness associated with loss of weight had developed. At intervals he suffered from severe sweats. The right testicle continued to increase in size and a diagnosis of tuberculosis was made. A right orchidectomy was performed on November 5, 1936. Following this, the patient had a draining sinus for two and one-half months. His general condition did not improve, and a few weeks before coming to the Clinic the left testicle became painful and enlarged.

Physical examination revealed no apparent abnormalities except for absence of the right testicle. The left epididymis was thickened and tender. The prostate was slightly enlarged, very firm and smooth, and the left lobe was somewhat tender. The right hand showed changes characteristic of rheumatoid arthritis.

Roentgen examination of the chest revealed an old right basal fibrosis. The spine showed an old left lumbar scoliosis with rotation and extensive osteoarthritis.

Laboratory findings: Examination of the blood showed 4,550,000 red cells per cubic centimeter, 5,500 white cells per cubic centimeter, and 90 per cent hemoglobin. The differential count was 70 per cent, polymorphonuclear neutrophils; 1 per cent, eosinophils; 29 per cent, lymphocytes. The level of the blood sugar was 112 mg. per 100 cc. and of the blood urea 42 mg. per 100 cc. The Wassermann and Kahn reactions of the blood were negative. Urinalysis gave normal findings. The sediment of the urine was negative for tubercle bacilli. The sedimentation rate was increased to 1.08 mm. per minute. The agglutination test for Brucella abortus was positive in a dilution of 1:160.

On further questioning of the patient, it was learned that abortions had occurred quite frequently among his cattle, so in all probability the animals were a source of infection. After an evaluation of the history, clinical, and laboratory findings, a diagnosis of undulant fever was made and it was decided to give the patient artificial fever therapy.

Figure 1 shows the temperature curve before and after fever therapy. The patient received three artificial fever treatments. The temperature during the

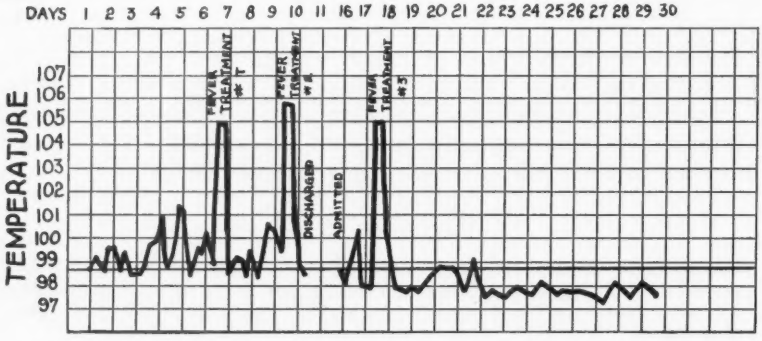

FIGURE 1

first treatment ranged between 104° and 105° F. for five hours. The second and third treatments were given between 105° and 106° F. for five hours each. The fevers were produced by electromagnetic induction. Figure 2 shows a graph of the second treatment.

Four months after the last fever treatment, the patient's general physical condition has improved greatly. His temperature has remained normal and he has gained about 15 pounds in weight. Some of the symptoms of arthritis still persist in the joints.

COMMENT

Another patient has just completed three artificial fever treatments for undulant fever, but it is too early to make any statements as to the final result. However, the results obtained thus far in a limited number of patients indicate that this form of therapy is of definite value in the treatment of patients with undulant fever and it certainly should be used until more data are available.

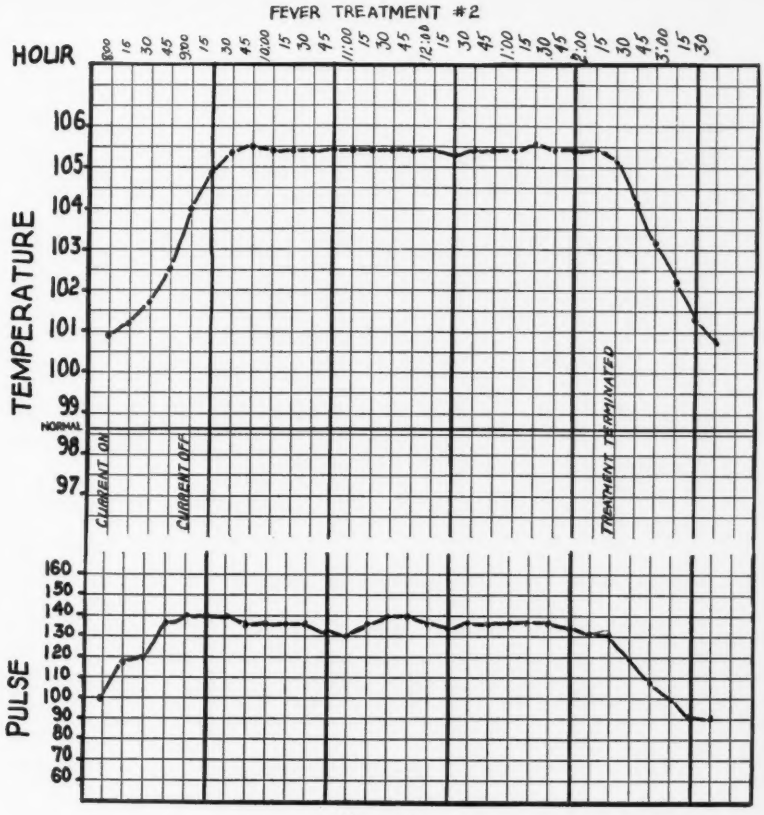

FIGURE 2

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1. Angle, F. E.: Treatment of acute and chronic brucellosis (undulant fever); personal observation of 100 cases over a period of 7 years, J.A.M.A., 105:939-942 (September 21) 1935.

2. Prickman, L. E. and Popp, W. C.: Treatment of brucellosis by hyperpyrexia induced by the Simpson-Kettering hypertherm, Proc. Staff Meet. Mayo Clin., 11:506-510 (August 5) 1936.

THE FRANK E. BUNTS INSTITUTE

As announced in the July issue of the Quarterly, The Frank E. Bunts Institute will offer a course in "Diseases of the Skeletal and Nervous Systems" on Monday, Tuesday, and Wednesday, November 8, 9, and 10, 1937.

A complete outline of the course and an application blank will be found on succeeding pages of this Quarterly.

DISEASES OF THE SKELETAL SYSTEM

Monday, November 8, 1937

8:30 A. M.	Registration	
9:00 A. M.—10:30 A. M.	Fractures of the Upper Extremity	J. I. KENDRICK, M. D.
10:30 A. M.—12:00 Noon	Fractures of the Lower Extremity	J. A. DICKSON, M. D.
12:00 Noon—12:15 P. M.	Demonstration of Reduction of Fractured Spine	J. I. KENDRICK, M. D.
12:15 P. M.— 1:00 P. M.	Luncheon	
1:00 P. M.— 1:30 P. M.	Exhibits	
1:30 P. M.— 2:30 P. M.	Demonstration of Orthopaedic Cases	
2:30 P. M.— 3:00 P. M.	Periarthritis of the Shoulder	J. A. DICKSON, M. D.
3:00 P. M.— 4:00 P. M.	Low Back Pain	J. I. KENDRICK, M. D.
4:00 P. M.— 5:00 P. M.	Derangement of the Knee Joint	J. A. DICKSON, M. D.
6:00 P. M.	Dinner	
8:15 P. M.	Frank E. Bunts Lecture: Fractures of the Lower Leg and Ankle	W. B. CARRELL, M. D., Professor of Orthopaedic Surgery, Baylor University College of Medicine, Dallas, Texas.

Tuesday, November 9, 1937

9:00 A. M.— 9:45 A. M.	Differential Diagnosis of Arthritis	RUSSELL L. HADEN, M. D.
9:45 A. M.—10:30 A. M.	Medical Treatment of Arthritis	RUSSELL L. HADEN, M. D.
10:30 A. M.—12:00 Noon	Orthopaedic Treatment of Arthritis.	
	Mechanical Prevention and Correction of Deformity	J. I. KENDRICK, M. D.
	Physiotherapy	WALTER J. ZEITER, M.D.
	Surgical Procedures	J. A. DICKSON, M. D.
12:00 Noon—12:15 P. M.	Visit to Physiotherapy Department	
12:15 P. M.— 1:00 P. M.	Luncheon	

Tuesday, November 9, 1937—Continued

DISEASES OF THE NERVOUS SYSTEM

1:00 P. M.— 2:00 P. M.	Demonstration: Technic of Lumbar Puncture	
2:00 P. M.— 3:00 P. M.	Neurosurgical Measures for the Relief of Pain	A. T. Bunts, M. D.
3:00 P. M.— 4:00 P. M.	Diagnosis and Treatment of Brain Tumors	W. James Gardner, M. D.
4:00 P. M.— 5:00 P. M.	The Hemiplegias	Louis J. Karnosh, M. D.
6:00 P. M.	Dinner	
8:15 P. M.	Frank E. Bunts Lecture: Diagnosis and Treatment of Acute Craniocerebral Injuries	Donald Munro, M. D., Assistant Professor of Neurological Surgery, Harvard University Medical School.

Wednesday, November 10, 1937

9:00 A. M.— 9:45 A. M.	Treatment of the Sequelae of Cranial Trauma	W. James Gardner, M. D.
9:45 A. M.—10:30 A. M.	Cerebrospinal Syphilis	E. W. Netherton, M.D.
10:30 A. M.—11:15 A. M.	The Eye and Neurology	A. D. Ruedemann, M.D.
11:15 A. M.—12:15 P. M.	Virus Infections of the Central Nervous System	John Tucker, M. D.
12:15 P. M.	Luncheon	
1:00 P. M.— 2:00 P. M.	Diseases of the Peripheral Nerves	Louis J. Karnosh, M. D.
2:00 P. M.— 3:00 P. M.	Surgical Lesions of the Spinal Cord	A. T. Bunts, M. D.
3:00 P. M.— 4:00 P. M.	Management of the Nervous Patient	C. L. Hartsock, M. D.

Exhibits

Orthopaedic Exhibits	*Neurological Exhibits*
Bone Lengthening	Encephalography and Ventriculography
Bone Dyscrasias	Surgical Treatment of Spasmodic Torticollis
Torticollis	Neurosurgical Technic
Arthritis	Von Recklinghausen's Disease
Bone Tumors	Hereditary Bilateral Acoustic Tumors
Epiphysitis	Histological Types of Brain Tumors
Scoliosis	Motion Pictures of Certain Neurological Disorders
Dupuytren's Contracture	

REGISTRATION BLANK

....., 1937

THE FRANK E. BUNTS INSTITUTE
Cleveland Clinic
Cleveland, Ohio

Gentlemen:

Please register me for the course in "Diseases of the Skeletal and Nervous Systems" which is to be given November 8, 9, and 10, 1937.

I am enclosing a check for $5.00 and the remainder of the fee, $5.00, will be paid on registration, November 8.

Name .....

Address .....

.....
Medical School from which graduated

Note: Checks should be made payable to The Frank E. Bunts Institute and sent to A. D. Ruedemann, M. D., Cleveland Clinic, Cleveland, Ohio.

The Frank E. Bunts Institute

THE Frank E. Bunts Institute, in conjunction with the Cleveland Ophthalmological Society, announces a course in Ophthalmology on December 6, 7, and 8, 1937.

On December 9, 10, and 11, a course in Diseases of the Ear, Nose, and Throat will be presented.

The fee for the two courses will be $25.00, or if only one course is taken, it will be $15.00.

A program of the course may be secured from A. D. Ruedemann, M. D., Chairman, Frank E. Bunts Institute, Cleveland Clinic, Cleveland, Ohio.

REGISTRATION BLANK

....., 1937

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Cleveland Clinic
Cleveland, Ohio

Gentlemen:

☐ Please register me for the courses in Ophthalmology and Diseases of the Ear, Nose. and Throat which are to be given December 6, 7, 8, 9, 10, and 11, 1937. I am enclosing a check for $5.00 and the remainder of the fee, $20.00, will be paid on registration, December 6.

☐ Please register me for the course in Ophthalmology which is to be given on December 6, 7, and 8, 1937. I am enclosing a check for $5.00, and the remainder of the fee, $10.00, will be paid on registration, December 6.

☐ Please register me for the course in Diseases of the Ear, Nose, and Throat which is to be given December 9, 10, and 11, 1937. I am enclosing a check for $5.00 and the remainder of the fee, $10.00, will be paid on registration, December 9.

Note: Checks should be made payable to The Frank E. Bunts Institute and sent to A. D. Ruedemann, M. D., Cleveland Clinic, Cleveland, Ohio.

Name .....

Address .....

.....

Medical School from which graduated.

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